**DOCTOR OF MEDICINE**

# Studies of psoriatic arthritis

Jones, Sharon Mary

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# STUDIES OF PSORIATIC ARTHRITIS

An investigation into the link between joint, skin and nail disease in psoriatic arthritis - a clinical, radiological, genetic and immunohistological study.

Dyslipoproteinaemia in psoriatic arthritis: identification of an atherogenic profile with active joint disease.

**Submitted by**

**SHARON MARY JONES**

**for the degree of MD**
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ProQuest LLC
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106-1346

For Graeme, Sophia and Imogen

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# PREFACE

This thesis describes research started while I was a Research Fellow at the Bath Institute for Rheumatic Diseases from April 1993 to May 1995. The Institute is associated with the University of Bath and Royal National Hospital for Rheumatic Diseases. The work was completed part-time whilst I held a Senior Registrar post at the same hospital from June 1995 to May 1998.

The thesis contains a number of closely linked studies designed to increase our understanding of the link between joint, skin and nail disease in psoriatic arthritis and factors which may influence its onset, progression and outcome. The studies use clinical descriptive, epidemiological, immunohistological and immunogenetic techniques.

A brief general summary, including major research goals, results and interpretation of each study, precedes a general introduction which surveys the literature which lead to the hypothesis and study aims. Full details of the methods and results of each study are reported together to aid comprehension. They are collected into three distinct chapters reflecting broad research thrusts. Each section of chapter 2 and chapters three and four are preceded by structured summaries and brief introductions. A short discussion completes each section so that each section of chapter 2 and chapters 3 and 4 are complete in themselves. The results of the studies are synthesised in a concluding general discussion, which draws on contemporary research to assist evaluation, and outlines possible areas for future research.

## ACKNOWLEDGEMENTS

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Finally I would like to thank my husband without whose unending patience, encouragement and practical help this work would never have been completed.

# ABBREVIATIONS

| | |
|---|---|
| ANA | antinuclear antibodies |
| AS | ankylosing spondylitis |
| CLA | cutaneous lymphocyte antigen |
| CRP | C-reactive protein |
| DIP | distal interphalangeal |
| DMARD | disease-modifying anti-rheumatic drug |
| ERO | erosions |
| E-selectin | endothelial selectin |
| ESR | erythrocyte sedimentation rate |
| HAQ | health assessment questionnaire |
| HDL | high density lipoprotein |
| IP | interphalangeal |
| JSA | joint space abnormality |
| LDL | low density lipoprotein |
| Lp(a) | lipoprotein (a) |
| MCP | metacarpophalangeal |
| MHC | major histocompatibility complex |
| NSAID | non-steroidal anti-inflammatory drug |
| OA | osteoarthritis |
| PASI | psoriasis area and severity index |
| PIP | proximal interphalangeal |
| PsA | psoriatic arthritis |
| RA | rheumatoid arthritis |
| RF | rheumatoid factor |
| SD | standard deviation |
| SE | shared epitope |
| SEM | standard error of the mean |
| SF | synovial fluid |
| SM | synovial membrane |
| SMR | standardised mortality ratio |
| TNF | tumour necosis factor |
| VLDL | very low density lipoprotein |

## SUMMARY

The first part of this thesis focuses on the clinical expression and natural history of psoriatic arthritis, the relationship of joint disease to skin and nail disease and the identification of factors that may predict disease progression. The pattern of disease was documented in 100 patients attending a psoriatic arthritis clinic in whom the mode of onset was known. These patients were prospectively followed up at five years. The mode of onset did not predict outcome in the majority, the majority of patients progressing from oligoarthritis to polyarthritis. After five years, the peripheral joint disease of many of these patients continued to deteriorate both clinically and radiologically. Hence peripheral joint disease in psoriatic arthritis is progressive in the majority of patients and requires effective monitoring and treatment.

There was no association between the severity, activity or type of skin disease and the severity or activity of joint disease either at the initial presentation or five year follow-up although 23/87 patients reported simultaneous exacerbations of their skin and joint disease. A separate prospective study of 24 patients who were documented at regular intervals showed that simultaneous exacerbations occurred only slightly more often than would be expected by chance, and this characteristic did not define a separate subgroup of patients. The number of patients with nail disease increased with time, nail disease was more common in patients with DIP joint disease and was significantly associated with adjacent DIP joint disease, suggesting a common local inflammatory mechanism.

There was a significant positive correlation between the initial viscosity and rate of progression of joint damage, suggesting that a raised plasma viscosity may be a predictive factor. The prevalence of the rheumatoid arthritis HLA DR1 and DR4 'shared epitope' was similar in psoriatic arthritis to a control population and was

unrelated to disease pattern or progression. This further distinguishes psoriatic arthritis from rheumatoid arthritis. Pregnancy and other hormonal factors may trigger or modify peripheral joint disease in some women.

The second part of this thesis focuses on immunological mechanisms that may explain the link between joint and skin disease in psoriatic arthritis. The study investigated whether skin-homing T lymphocytes identified by the cutaneous lymphocyte antigen (CLA) are increased in the synovial membrane of patients with psoriatic arthritis. Synovial samples were obtained from involved knees and lesional skin biopsies were taken from patients with psoriatic arthritis and psoriasis alone. All samples were single and dual-stained for CLA and CD3, a T cell marker, using monoclonal antibodies. The ligand for CLA on endothelial cells is E-selectin and its expression was also determined. The percentage of dual-stained lymphocytes was significantly greater in psoriatic skin than in synovium and similar between psoriatic and rheumatoid synovium. There was no significant difference in the percentages of CLA-positive cells in psoriatic skin in patients with psoriatic arthritis compared with psoriasis alone. The intensity of endothelial E-selectin expression was significantly greater in skin psoriasis than in synovium, and rheumatoid synovium had significantly greater expression of E-selectin than psoriatic synovium. However, there was no significant correlation between E-selectin expression and the percentages of CLA-positive lymphocytes. This study provides further evidence that the CLA antigen is enriched on skin-homing lymphocytes. Conversely, the link between skin and joint inflammation in psoriatic arthritis does not seem to be explained by increased trafficking of CLA T cells to psoriatic synovium.

Other factors may influence the morbidity and mortality of patients with psoriatic arthritis. In the third and final study of this thesis, the lipid profile in psoriatic arthritis is characterised in relation to a control population to determine whether there is an atherogenic lipid profile in psoriatic arthritis, which may have a bearing

on mortality. Fasting lipids, lipoproteins and their subfractions were measured in 50 patients with psoriatic arthritis and their age and gender matched controls. High density lipoprotein-cholesterol (HDL-cholesterol) and, specifically, its third subfraction, HDL-3-cholesterol, were significantly reduced in the psoriatic arthritis patients. The most dense subfraction of low density lipoprotein (LDL), LDL-3, was significantly increased in the psoriatic arthritis patients. Twenty patients with active synovitis had significantly lower total cholesterol, LDL-cholesterol and HDL-3-cholesterol than their controls. Twenty-five per cent of the psoriatic arthritis patients had elevated Lipoprotein (a) (Lp(a)) levels (> 300mg/l) compared with 19% of controls.

In conclusion, elevated levels of LDL-3 combined with low levels of HDL-cholesterol, in addition to Lp(a) levels > 300mg/l, are associated with coronary artery disease. This atherogenic profile occurs in PsA, which may be associated with accelerated mortality.

# CHAPTER 1

# GENERAL INTRODUCTION

Psoriatic arthritis has a long history:- there are reports of its existence in a fifth century Judean monastery (Zias and Mitchell 1996), and characteristic radiographic features have been observed in medieval skeletons (Rogers et al 1982). The association between psoriasis and joint disease was first recognised by Alibert in 1822 and later coined "Psoriasis Arthritique" by Bazin (1860) although the inflammatory, proliferative skin lesions were thought to be lepromatous. Bourdillon is credited with proposing its existence in his Doctoral Thesis (Bourdillon 1888). He noted the typical involvement of the distal interphalangeal joints of the hands and feet, which seemed to distinguish psoriatic arthritis from other rheumatic diseases.

Throughout the 1950s and 1960s, a number of studies have indicated a significant association between psoriasis and arthritis (Vilanova and Pinol 1951, Coste et al 1958, Wright 1959a and 1959b, Bauer 1965). The prevalence of psoriasis in arthritis patients is 2.6 to 7%, whereas psoriasis has a prevalence of 1.5-3% (Camp 1992). The prevalence of arthritis in the general population is 2 - 3%, while in psoriatic patients it has varied from 7 to 42% in different populations (Gladman 1993a and 1994), although 5% is still quoted by some (Pitzalis 1996). The overall prevalence of psoriatic arthritis may therefore approach that of rheumatoid arthritis and ankylosing spondylitis.

Despite the antiquity of psoriatic arthritis and strong epidemiological evidence, its existence as a specific entity is still questioned by some (Van Roumude et al 1984a, b and c; Cats 1990). Also the distinction of psoriatic arthritis from rheumatoid arthritis and its relationship to the sero-negative spondyloarthritides have remained a subject of debate. It was the discovery of rheumatoid factor and its absence in the

majority of patients with psoriasis and arthritis that lead to its recognition as a distinct entity by the Arthritis and Rheumatism Council in 1964 (Blumberg et al 1964). Nevertheless, the precise definition of psoriatic arthritis remains controversial, with rheumatoid factor positivity used as an exclusion criteria by some (Wright 1956), but not others (Gladman et al 1986, 1995a and b; Little et al 1975, Leonard et al 1978, Kammer et al 1979). Psoriatic arthritis usually differs from rheumatoid arthritis in its clinical presentation, which is often asymmetrical, the presence of distal joint diseases, and the presence of a spondyloarthritis, with no gender predilection. In some patients, the controversial issue of whether the diagnosis is psoriatic arthritis or rheumatoid arthritis with psoriasis, cannot be resolved (Helliwell and Wright, 1994). However, the discovery that rheumatoid arthritis improves with the depletion of T helper lymphocytes secondary to HIV infection, whereas psoriasis or psoriatic arthropathy get worse (Espinoza et al 1988, Arnett 1991, Espinoza et al 1992a) supports the distinction between the two diseases. Furthermore, family studies have been important in establishing the concept of the sero-negative spondyloarthritides including ankylosing spondylitis, Reiter's syndrome, enteropathic arthropathies as well as psoriatic arthritis, which share common clinical features and have an increased frequency of HLA B27 (Moll et al 1974; Wright and Moll 1976; Eastmond 1994; Moll 1994, Alenius 1997). Clinically, psoriatic arthritis when it occurs with pustular psoriasis may be indistinguishable at onset from Reiter's syndrome with keratoderma blenorrhagia although Reiter's syndrome tends to be a more systemic illness (Keat 1994). Similarly patients with a spondyloarthropathy and psoriasis may resemble idiopathic ankylosing spondylitis in the expression of their joint disease. However psoriatic arthritis has unique features which include the predominance of a characteristic peripheral arthropathy and spondyloarthropathy which is less symmetrical, causes less spinal dysfunction and differs radiologically from ankylosing spondylitis. In addition, HLA B27 is present in less than 50% of patients with psoriatic arthritis.

Therefore psoriatic arthritis may be considered to be a disorder distinguishable from both rheumatoid arthritis and ankylosing spondylitis.

Psoriatic arthritis has been divided into subgroups according to the distribution and number of joints involved. In 1941, two clinical patterns were defined (Bauer et al 1941, Sherman 1952) - 1. an arthritis with rheumatoid-like features; 2. an arthritis exclusively involving the DIP joints associated with nail disease. The original five subgroups described by Moll and Wright may still be the most widely used in clinical practice: 1. asymmetrical, oligoarticular arthritis chiefly affecting the MCPs. PIPs and DIPs and associated with sausage digits (70%); 2. symmetrical, rheumatoid-like arthritis distinguishable from rheumatoid arthritis by DIP involvement and negative rheumatoid factor (15%); 3. the 'classical' pattern of psoriatic arthritis in which the DIP joints are predominantly involved and nail changes are invariable (5%); 4. arthritis mutilans, a severe deforming arthritis affecting young patients in which sacroileitis is frequently present (5%); 5. spondylitis in which symptoms may be minimal despite marked radiological changes (5%) (Moll and Wright, 1973). The distinctions between these subgroups are controversial, and difficult to apply consistently in research studies . Others have proposed fewer subgroups (Kammer et al 1979, Veale et al 1994, Helliwell et al 1991). Kammer et al (1979), and later Veale et al (1994), emphasised the rarity of exclusive DIP joint involvement, its presence in other subgroups, and the frequent overlap of mutilans with all other articular forms of arthritis. Kammer et al described an oligoarthritis group (frequently asymmetrical), a symmetrical arthritis and a spondyloarthritis. Based on radioisotope bone scanning, Helliwell et al (1991) also proposed three subgroups, a large group with peripheral arthritis, a group with predominant spondylitis and a group with extra-articular osseous manifestations, closely linked to the SAPHO syndrome (see below). Gladman et al (1986) described seven subgroups based on the association with immune response genes and recognising patients with an overlap of spondylitis and peripheral arthritis belonging

to DIP, oligoarticular or polyarticular groups. Gladman et al (1987) later described the disease as a heterogeneous spectrum of features and severities, although has continued to use seven subgroups in later studies (Gladman, 1995a and b). Whatever subgroup classification is used, it is unclear whether the subgroups are homogeneous or whether they become established at some stage in the course of the disease. In Chapters 2a and b subgroup homogeneity is assessed both by retrospective study of the mode of presentation of 100 patients and by prospective five year follow-up of these patients.

Historically, psoriatic arthritis has been considered to be a milder form of arthritis than rheumatoid arthritis with short-lived synovitis, involving less pain and residual damage and consequent disability in the majority of patients (Scarpa et al 1984 and 1992b, Oriente 1994). Wright compared patients with psoriasis and erosive arthritis with classical rheumatoid arthritis and noted that psoriatic arthritis was less often polyarticular at onset and tended to be less severe than rheumatoid disease with fewer affected joints and fewer deformities (Wright 1956). Kammer et al (1979) studied 100 patients with psoriatic arthritis and found the asymmetrical oligoarticular pattern to be most prevalent. They suggested that the disease course in this subgroup was less aggressive and disabling than that in other forms of psoriatic arthritis. Patients with symmetrical arthritis were more likely to develop destructive and potentially deforming disease, and the majority were women. Although there are certainly fewer extra-articular features than either rheumatoid arthritis or ankylosing spondylitis, there has been little further evidence to suggest that the arthritis is less severe in terms of deforming radiological changes or disability. Evidence for this is that erosive disease has been reported in up to 57% (Torre Alonso et al 1991) and a follow-up study revealed that polyarthritis became more common, the majority had an arthritis indistinguishable from rheumatoid arthritis, 16% had DIP disease and 5% a mutilating arthritis (Roberts et al 1976, Wright 1992). Later cross-sectional work by others has consistently found polyarthritis to be the most common, although the

pattern of arthritis in many of these patients may be asymmetrical and not rheumatoid-like (Scarpa et al 1984, Gladman et al 1987, Veale et al 1994). Clinically, psoriatic arthritis may appear to be less severe than rheumatoid arthritis because there is less joint tenderness (Buskila et al 1992). It is well recognised however that pain may not be directly related to joint damage and deformity. This is illustrated by the recent observation that arthritis mutilans, the most severe consequence of psoriatic arthritis, with telescoping of the digits and the 'opera-glass' hand, may be associated with Charcot joints (Cuéllar et al 1996).

The detailed natural history of psoriatic arthritis, the homogeneity of disease subgroups, and predictive factors for disease progression have been infrequently studied (Gladman et al 1994 and 1995a and b). In rheumatoid arthritis, radiographic changes in the hands have been found to reflect clinical joint damage and progression, and have been used as important outcome measures in therapeutic trials (Kirwan 1995). However, data on the pattern and rate of progression of radiological changes in the hands in patients with psoriatic arthritis is limited (Roberts et al 1976, Gladman et al 1990). A thorough understanding of the natural history of a disease is an essential prerequisite for the prediction of outcome. The heterogeneity of psoriatic arthritis make the establishment of reliable predictive factors particularly complex and important. Furthermore there has been a tendency to avoid giving disease modifying medication in patients with psoriatic arthritis, a fact that is reflected in the paucity of drug trials in psoriatic arthritis (Gladman 1992). Prognostic indicators are vital for both patients and rheumatologists, influencing both follow-up and treatment decisions. Some of these factors are addressed in Chapter 2b.

Clinical descriptive and epidemiological studies have conclusively established a link between psoriasis, nail disease and arthritis. However, the precise relationship between the three manifestations of the disease remains uncertain. Some individuals, 20% in most studies, present with joint symptoms before skin lesions appear

whereas, in the majority, up to 80%, skin problems manifest themselves first. Psoriasis tends to be more severe in patients with psoriatic arthritis and nail disease tends to be more common (Camp 1992). The temporal relationship between the activity and severity of joint disease and the activity and extent of skin disease and nail disease has never been assessed prospectively. Gladman reported that 35% of patients have simultaneous exacerbations of skin and joint disease (Gladman et al 1987), but the data was not obtained prospectively, although the figure has often been quoted in reviews (Gladman 1994). It is unclear whether the severity of skin disease may be an independent prognostic factor for psoriatic arthritis. It is possible that there may be a subset of patients with psoriatic arthritis, distinguished by simultaneous exacerbations of their disease that share a common immunogenetic profile. The aims of the study presented in Chapter 2c was to prospectively evaluate the temporal association of skin and joint involvement. The frequency of simultaneous exacerbations of joint, skin and nail disease was assessed in patients attending the psoriatic arthritis clinic who had active skin and joint disease at baseline.

Many of the genes implicated in susceptibility to rheumatic conditions map to the major histocompatibility complex (MHC) at the centromeric end of the short arm of chromosome six (Stastny et al 1983). Several genes in this region are essential to the mounting of normal cellular and humoral inflammatory responses. The human leucocyte antigen (HLA) genes are a small component of this region. There are three primary elements involved in initiating a specific immune response - an HLA Class I or Class II molecule, an antigen (in the form of a peptide) that associates in the antigen-binding site of the HLA Class II molecule, and the T-cell antigen receptor found on the surface of all T cell populations. The MHC can be divided into three regions, Classes I to III, each containing a series of homologous loci. Encoded within the Class II region are the classical Class II genes, HLA-DR, -DQ and -DP. Each Class II molecule is a trans-membrane glycoprotein heterodimer, consisting of

a non-covalently bound α - and β - chain. Polymorphism of the HLA-DR molecule is confined to DR β chains, encoded at several distinct loci (Bell et al 1989).

Genetic susceptibility is likely to be of major importance in the development of psoriatic arthritis and may be critical in determining its pattern of expression and severity. HLA typing has been used to identify the role of HLA genes in susceptibility to diseases by comparing the prevalence of certain specificities among patient populations and healthy controls (Tiwari and Terasake 1985). To date, HLA studies in psoriatic arthritis have been performed primarily using serologic techniques. The associations have generally been with Class I antigens, encoded by the A, B and C loci of the MHC. Class II antigens, encoded by the HLA-D loci of the MHC have also been studied in psoriasis and psoriatic arthritis. The associations of the MHC Class I molecules are well established, with B13, B17, B27 and Cw6 occurring with increased frequency in both psoriasis and psoriatic arthritis (Al - Jaralah et al, 1993; Eastmond 1994) and HLA B16 and its splits B38 and B39 occurring in association with psoriatic arthritis (McHugh et al 1987, Gladman et al 1995a). In psoriasis, it has been established that HLA Cw6 is the primary association and that the other HLA Class 1 associations are in linkage disequilibrium with this allele (Green et al 1988). Of the immunoresponsive MHC Class II molecules, HLA-DR7 has been consistently found to be increased in both psoriasis and psoriatic arthritis (Armstrong et al 1983, McHugh et al 1987, Espinoza et al 1992, Gladman et al 1995a). In psoriatic arthritis HLA-DR4 has been found to be associated with peripheral arthritis resembling rheumatoid arthritis by some (Gerber et al 1982, Kanter et al 1984, Espinoza et al 1982 and 1985) but not others (Beaulieu et al 1983, McKendry et al 1984, Gladman et al 1986, Salvarani et al 1989), and has been associated with erosive disease (McHugh et al, 1987). HLA-DR1 has also been found to be increased in some studies (Armstrong et al 1983).

It has been established for over 20 years that certain HLA-DR4 and HLA-DR1 serotypes are associated with the presence of rheumatoid arthritis in different populations. The further definition of HLA-DR4 and HLA-DR1 subtypes and the discovery that not all subtypes are associated with rheumatoid arthritis has lead to the "shared epitope" hypothesis (Gregarson 1987). This provides an explanation for the population association between rheumatoid arthritis and different, serologically defined class-II antigens at the DR loci on the basis of the 'shared possession' of a short sequence of amino acids in the third hypervariable region of the DRB1 gene. In rheumatoid arthritis, several authors have reported a hierarchy of disease susceptibility with a more pronounced association with 0401 (Dw4) and 0404 (Dw14). Also, there is good evidence that HLA-DR4 is associated with disease severity, with increased representation in patients with rheumatoid arthritis attending hospital specialists (van Zeben et al 1991). Homozygosity for the 'shared epitope' or compound heterozygosity (two different alleles containing the 'shared epitope') has been found to be linked to severe erosive disease (McDonagh et al 1997). All previous HLA studies in psoriatic arthritis used serological immunocytotoxicity techniques, so did not examine genetic subtyping in sufficient detail to evaluate the "shared epitope" hypothesis.

The objectives of the study presented in Chapter 2d were therefore to determine whether the 'shared epitope' conferred susceptibility or was linked to the severity of psoriatic arthritis. Specifically, I wished to determine to prevalence of HLADRB1 alleles and the "shared epitope" in hospital outpatients with psoriatic arthritis compared with healthy controls and to determine the association of the "shared epitope" with subgroups of disease and erosive disease, and the progression of joint scores and erosions over five years.

Hormonal factors may also have a role in determining outcome in psoriatic arthritis. There is a growing awareness of the role of pregnancy and other hormone-associated

events in influencing the onset, expression and outcome of rheumatic diseases, particularly systemic lupus erythematosus and rheumatoid arthritis which both have a marked female predominance (Petri et al 1997, Buyan et al 1993, Østensen and Lee Nelson 1995). Onset of rheumatoid arthritis closely related to pregnancy has been described and a greater than five-fold increase in risk of rheumatoid arthritis onset during the first 3 months post-partum has been reported, particularly following the first pregnancy (Silman et al, 1992). In rheumatoid arthritis post-partum onset is positively associated with breast feeding, possibly related to hyperprolactinaemia.

There have been fewer studies in the sero-negative spondyloarthropathies, including psoriatic arthritis, but it has been suggested that hormone-associated events may also be important modifiers of the disease (Østensen and Husby, 1983 and Østensen, 1992). A preliminary study of 15 mothers with psoriatic arthritis suggested that pregnancy may trigger an earlier onset of psoriatic arthritis in the post partum period (McHugh and Laurent 1989). Both retrospective and prospective work by Ostensen, found that the pregnancy related remissions and post-partum flares of peripheral joint disease occurred in psoriatic arthritis (Østensen 1992). The aims of the study presented in Chapter 2e was to assess the relationship between hormonal-associated events including pregnancy, menstruation and the menopause and the onset and expression of arthritis and psoriasis in psoriatic arthritis.

A topographic relationship between nail and DIP joint disease was noted in some of the earliest studies of psoriatic arthritis, but not statistically analysed (Wright 1956). In Chapter 2a, a statistically significant topographic association between nail and DIP disease is demonstrated, demanding a pathophysiological explanation for the link. Although the inflammatory processes which link skin, nail and joint disease remain elusive, an immune-mediated pathology is implicated. Decker described "noxious substances" that may traffic from the nail to the joint and our understanding of the immunological processes involved in linking joint, skin and

nail involvement has evolved little to date (Decker 1985). However the infiltration of skin and synovial tissue with mononuclear cells including T lymphocytes, an association with major histocompatibility antigens, and the response to immunotherapy all suggest an immune-mediated pathology.

Immunopathogenic mechanisms involving T lymphocytes in psoriasis and arthritis appear similar. Both the skin and synovium are infiltrated with activated T lymphocytes (Barker 1994, Panayi 1994) with a preponderance of CD4RO+ve cells, which are known to migrate preferentially to peripheral tissues (Panayi 1994). The associations with major histocompatibility haplotypes, the only known function or which is to present antigen to T cells, have been summarised above and further assessed in Chapter 2d (NcHugh et al 1987, Eastmond et al 1994). Both psoriasis and arthritis increase in severity with the depletion of T helper lymphocytes secondary to HIV infection (Espinoza et al 1992a, Arnett et al 1991, Keat 1994) and both improve in response to immunotherapy such as cyclosporin A (Salvarani et al 1992a).

The skin is a functionally unique immune site with apparently a specific homing mechanism for T cells. The cutaneous lymphocyte antigen (CLA), defined by the monoclonal antibody HECA-452 identifies a population of skin-homing memory T cells (Picker et al 1990). The receptor for CLA on dermal endothelium is the inducible cell adhesion molecule E-selectin (Picker et al 1991), a protein which also acts to tether neutrophils during their initial rolling interaction with the blood vessel wall at the onset of an inflammatory response (Bevilacqua et al 1994, Berg et al 1991). It has been proposed that E-selectin on venules at sites of acute inflammation supports neutrophil recruitment, whereas in sites of chronic inflammation in the skin mediates accumulation of CLA-positive T cells (Picker et al 1991).

The principal aim of the study presented in Chapter 3 is to determine whether skin and joint disease in psoriatic arthritis may be linked through the inappropriate expression of CLA molecules, E selectin or both. I have therefore investigated the percentages and distribution of skin-homing (CLA-positive) T lymphocytes and their counter-receptor E-selectin in the skin, synovium and peripheral blood of patients with psoriatic arthritis and appropriate controls.

Metabolic factors may also be of significance in the management and ultimate outcome of psoriatic arthritis patients. Patients with rheumatoid arthritis have an accelerated mortality compared with the general population, which may be attributed in part to an increased risk of cardiovascular disease (Pincus 1995a). Active rheumatoid arthritis is associated with an abnormal lipid profile (dyslipidaemia), although the relative contribution of this to the increased mortality is uncertain. Altered concentrations of serum lipids and lipoproteins (London et al 1963, Rossner and Lofmark 1977, Lorber et al 1985, Lazarevic et al 1992, Svenson et al 1987), and synovial lipids (Winyard et al 1993) and lipoproteins may occur including a reduced serum cholesterol (London et al 1963), decreased serum triglycerides (Rossner and Lofmark 1977, Lorber et al 1985, Lazarevic et al 1992, Svenson et al 1987) and altered apoprotein concentrations (Rossner and Lofmark 1977). In addition decreased cholesterol in LDL, and cholesterol in HDL have been found, especially in association with active disease (Lorber et al 1985). The causes of mortality in psoriatic arthritis patients is less well documented, although there is evidence that both psoriasis alone and psoriatic arthritis may be associated with an increased risk. The largest mortality study in psoriatic arthritis to date showed a 1.59 fold increased risk for death in women and 1.65 fold increased risk for men (Wong et al 1996). Thirty per cent of the deaths were from circulatory disease. A pattern of dyslipoproteinaemia similar to that seen in rheumatoid arthritis has previously been reported in psoriatic arthritis, which normalises with a reduction in disease activity (Lazarevic et al 1992).

Routine plasma lipid measurement, which does not take account of lipoprotein composition may not identify patients with risk factors for atherosclerosis. For instance, the reduction in HDL-cholesterol contributes to a risk of atheroma, whereas a concomitant reduction in LDL - cholesterol may be protective. Increased knowledge of lipoprotein composition and the identification of lipoprotein subfractions has added to our understanding of the mechanisms of metabolic disturbance in lipid disorders (Lindgren et al 1972). Detailed lipoprotein composition has not been previously measured in studies of arthritis. In population studies, a low HDL-cholesterol associated with a high LDL-cholesterol has been associated with an increased risk of atherosclerosis (Castelli et al 1986). Recently, it has been found that the smallest, most dense component of LDL, ( LDL-3), is the most important factor in contributing to atheroma (Austin et al 1988).

Lipoprotein (a) (Lp(a)) has emerged as an important and independent contributing factor to the risk of arteriosclerosis (Rosengren et al 1990, Terres et al 1995, Maher and Brown 1995). Lp(a) is a high density lipoprotein in which apo$B_{100}$, the protein moeity of LDL, is linked to apo (a) by one or two disulphide bridges. Increased levels of Lp(a) have been found in rheumatoid arthritis, but have not previously been measured in psoriatic arthritis (Rantapaa-Dahlqvist 1991).

The objectives of the study presented in Chapter 4 are 1. to characterise in detail lipoprotein composition, including Lp(a), in psoriatic arthritis and investigate whether there are similarities to the dyslipoproteinaemia reported in rheumatoid arthritis and other inflammatory forms of joint disease; 2. to investigate whether there is an atherogenic lipid profile in psoriatic arthritis, which may have a bearing on mortality.

To conclude, until recent years psoriatic arthritis has not been prominently featured in the clinical or scientific literature and this may be reflected in our lack of understanding of pathogenic mechanisms. Although there have been a number of clinical descriptive and family studies there has been little prospective work and few studies investigating the mechanisms linking skin and joint disease. The natural history of the disease and response to DMARDs remain uncertain. Also inadequate recognition of the disease by clinicians, and under representation by existing arthritis charities has lead to the institution of a patient support group, the Psoriatic Arthropathy Alliance. These factors have lead to the studies presented in this thesis.

## SUMMARY OF HYPOTHESES AND STUDY AIMS

The specific hypotheses and aims of my studies are:-

**Hypotheses 1: Chapter 2a**

(i) The mode of onset predicts outcome in psoriatic arthritis.
(ii) There is a significant association between nail and DIP joint disease in psoriatic arthritis.

**Study Aim: Chapter 2a**

To characterise the patterns of joint, skin and nail disease in the first 100 patients attending a psoriatic arthritis clinic, in relation to the reported mode of onset.

**Hypothesis 2: Chapter 2b**

Psoriatic arthritis is a progressive disease, with increasing joint involvement in the majority.

**Study Aim: Chapter 2b**

To perform a prospective 5 year clinical and radiological follow-up study the patients included in Chapter 2a.

**Hypothesis 4: Chapter 2c**

There is a temporal relationship between arthritis, psoriasis and nail disease in some patients, which may define a subset of disease.

**Study Aim: Chapter 2c**

To characterise prospectively the temporal relationship between skin and joint inflammation in psoriatic arthritis.

**Hypothesis 3: Chapter 2d**

Immunogenetic factors important in rheumatoid arthritis, i.e. the 'shared epitope' may influence susceptibility and severity in psoriatic arthritis, and may have implications for its pathogenesis.

**Study Aim: Chapter 2d**

To determine the frequency of the MHC class II 'shared epitope' in psoriatic arthritis and to relate the patterns of MHC Class II alleles to the pattern and progression of joint disease.

**Hypothesis 5: Chapter 2e**

Hormonal factors may influence the onset and expression of joint and skin disease in psoriatic arthritis.

**Study Aim: Chapter 2e**

To determine the relationship between pregnancy and other factors in influencing the onset and expression of skin and joint disease in psoriatic arthritis.

**Hypothesis 6: Chapter 3**

Selective T cell recruitment to skin and joint tissue and subsequent activation may explain the observed relationship between skin and joint disease in psoriatic arthritis.

**Study Aim: Chapter 3**

To investigate the distribution and characteristics of skin homing (CLA positive) T lymphocytes and their counter-receptor E-selectin in the skin and the synovium of patients with psoriatic arthritis.

**Hypothesis 7: Chapter 4**

Dislipoproteinaemia occurs in psoriatic arthritis and may be related to disease activity and atherogenic potential.

**Study Aim: Chapter 4**

To determine lipoprotein profiles in psoriatic arthritis and healthy age and sex matched controls.

# CHAPTER 2

The first part of this thesis focuses on the clinical expression of psoriatic arthritis, its natural history and the relationship of joint disease to skin and nail disease and predictive factors for disease progression.

# CHAPTER 2a

# PSORIATIC ARTHRITIS: OUTCOME OF DISEASE SUBSETS AND RELATIONSHIP OF JOINT DISEASE TO NAIL AND SKIN DISEASE: A CROSS-SECTIONAL STUDY

## SUMMARY

***Introduction.*** Subgroups of psoriatic arthritis have been described but their relationship to the mode of onset of arthritis, to distal interphalangeal joint disease and nail and skin disease remains controversial.

***Hypothesis*** . (i) The mode of onset predicts outcome in psoriatic arthritis. (ii) There is a significant association between nail and DIP joint disease in psoriatic arthritis.

***Study Aims.*** To characterise the patterns of joint, skin and nail disease in the first 100 patients attending a psoriatic arthritis clinic.

***Study Design.*** Cross-sectional, clinical observational, and retrospective.

***Methods.*** The pattern of disease was documented in the first 100 patients to attend a psoriatic arthritis clinic in whom the mode of onset was known. A proforma was completed on all patients including a standardised examination of joints, nails and skin, HAQ score and inflammatory markers. The patients were divided into six subgroups:- monoarthritis, DIP joint disease only, oligoarthritis, polyarthritis, spondyloarthropathy and arthritis mutilans.

***Results***. Sixty-four patients changed pattern. Nail disease (67% of total) was more common in patients with DIP joint disease (27% of total), and was significantly associated with adjacent DIP joint disease.

***Conclusions*** . The subgroup of onset did not remain constant with time, i.e. the mode of onset did not predict outcome in the majority of patients, and hypothesis (i) was disproven. The topographic association of nail and DIP joint disease suggests a common local inflammatory mechanism.

# INTRODUCTION

Psoriatic arthritis has been divided into subgroups by various authors according to the distribution and number of joints involved (Moll and Wright 1973, Kammer et al 1979, Gladman et al 1986, Helliwell et al 1991). It is unclear whether these subgroups are homogeneous with time. Also, relatively few series of patients have been reported in which the relationship between the skin, nails and joints has been adequately studied. The topographic relationship between nail and DIP joint disease has long been recognised but not statistically analysed (Wright 1956).

In the present study I have investigated whether the mode of onset of joint disease predicts the ultimate pattern of disease expression. I have also assessed in detail the relationship between nail and DIP joint disease, and patterns of skin and nail involvement in relation to the severity, activity and subgroups of joint disease.

# PATIENTS AND METHODS

### *Patients*

A clinic has been established at the Royal National Hospital for Rheumatic Diseases, Bath to study joint disease in patients with psoriasis. This section presents a cross-sectional study of the first 100 patients to attend this clinic in whom the mode of onset was known. All patients had an inflammatory arthropathy and psoriasis (Moll and Wright 1973, Bennett 1979, Gladman 1992b). The presence of rheumatoid factor was not used as an absolute exclusion criterion because of its lack of specificity for rheumatoid arthritis and its low prevalence in the normal population. The majority of patients were referrals from other rheumatology clinics, some were new referrals from the general practitioner and a minority (less than 10%) were referrals from dermatology clinics. All patients were seen by a rheumatologist and data were accumulated using a form designed specifically for the study.

### *Assertainment Bias*

The data from this study must be interpreted with knowledge of the inherent bias in the method of patient selection. This is a population of hospital outpatients, attending a clinic set up specifically for these patients, so does not represent a sample from the general practice population, and may not represent a population seen by other rheumatologists who do not have a specific interest in the condition. It is hoped that it may be representative of groups of patients attending other psoriatic arthritis clinics. In addition, patients with two diseases (arthritis and psoriasis) are more likely to attend hospital departments than patients with one disease, which has an impact on studies comparing these patients with those with one disease (eg rheumatoid arthritis, psoriasis alone), and in studies of mortality.

Females outnumbered males in this study by 57 to 43, whereas in the majority of studies of psoriatic arthritis, males have slightly outnumbered females or the sex

distribution has been equal. Ankylosing spondylitis is a major research interest in the Royal National Hospital for Rheumatic Diseases, lead by Dr Andre Calin. Male patients with psoriasis and arthritis in whom spondyloarthropathy is predominant (psoriatic spondylitis or ankylosing spondylitis with coincident psoriasis) are seen in Dr Calin's clinics. These patients may have been included in other series of psoriatic arthritis.

***Demographic Data and Joint Involvement***

The age of onset and the duration of psoriasis and arthritis, the family history, the mode and site of onset of joint disease and previous and current treatment were recorded.

The mode of onset referred to the joints involved within the first three months of symptoms; this information was usually well recalled by the patient and in most cases confirmed by documentation in the rheumatology case notes. However, I acknowledge that the absence of a complete record of objective clinical findings at onset may have resulted in an under estimate of the number and site of joints involved, particularly if some joints were significantly more severely involved than others. Conversely, some patients may have over estimated the number of involved joints if they experienced pain without objective clinical findings. The initial presentation was subdivided using three methods. Firstly five groups were identified; monoarthritis, DIP joint disease only, oligoarthritis (2 to 4 joints affected), polyarthritis (5 or more joints affected), and spinal disease. Secondly, the patients were divided by joint size into small joint (including hands and feet), large joints of the limbs, axial (including the spine and chest wall), and combinations of these. Thirdly, the patients were divided by anatomical region into upper limb, lower limb, spinal disease and combinations of these.

The number of involved or damaged joints was documented for each patient, using a method similar to that described by Gladman (Gladman et al 1987). The joint score ranged from 0 -70 with one point scored for each involved joint. The joints included were the DIP joints, IP joints of the thumbs, PIP joints, MCP joints, wrists, elbows, shoulders, temporo-mandibular, sterno-clavicular and acromio-clavicular, hips, knees, ankles (mortice joint), talocalcaneal, midtarsal, metatarsal-phalangeal joints, inter-phalangeal joint of the first toe and the remaining toes. The spine was excluded from this score although involvement of the cervical and lumbar spine was noted and used to assign the subgroup. The subgroup of joint disease was assigned in a similar way to that described above for the mode of onset, with the addition of arthritis mutilans as a sixth subgroup.

The activity of the peripheral joints was also documented for each patient. The number of tender joints was determined by a method or examination described by Ritchie in rheumatoid arthritis, but modified to include the DIP joints (Ritchie 1967). The number of swollen joints was also noted. A joint was considered to be active if it was tender and/or swollen.

Indices of peripheral joint disease activity and severity were obtained by counting the numbers of active or damaged peripheral joints and assessed as mild (0 to 10 joints), moderate (11-20 joints) or severe (>20 joints).

Although symmetry was not used to distinguish subgroups, symmetrical joint involvement was defined in two ways; firstly by at least one identical joint being involved on both sides of the body and secondly in a method devised by Helliwell et al (1991). In the latter method, the number of matched pairs of involved joints was related to the total number of matched and unmatched pairs and a ratio of 0.5 or greater defined symmetry. Functional assessment was made using the modified

Stanford Health Assessment Questionnaire (HAQ) (Kirwan and Reedback 1986, Fries et al 1980).

***Laboratory Data***

A rheumatoid factor, full blood count, plasma viscosity, anti-nuclear antibodies and immunoglobulins were performed on all patients.

***Skin and Nails***

The skin and nails were examined using a predefined protocol and performed under the supervision of a dermatologist (CL). Psoriasis was classified as plaque (psoriasis vulgaris), discoid, guttate, localised pustular or a combination of these. The distribution of skin psoriasis was recorded and the current severity was graded according to the Psoriasis Area and Severity Index (PASI) score (range 0 to 72) (Camp 1992, Appendix A). A nail score was determined for each patient, and derived as follows. Each fingernail was assessed for pitting, onycholysis, hyperkeratosis and severe nail deformity with involvement of both sides of the nail ("dystrophy"). Each of the listed features scored one with a possible maximum nail score of 40.

***Radiology***

Radiological evaluation was performed on clinically affected joints. The radiological protocol consisted of an anterior-posterior (AP) view of both hands and feet, lateral view of both heels, AP view of pelvis, AP view of lumbar spine (to include thoraco-lumbar junction) and a lateral view of the cervical spine in flexion. All films were examined by a radiologist (GE) and by two rheumatologists (NJM and SMJ). The five year follow - up study of hand radiology is reported in Section 2b. The cervical spine radiology has been published (Jenkinson et al 1994).

***Statistical Analysis***

All information was entered onto Excel Worksheets in a Workbook on an Apple Macintosh computer, creating a psoriatic arthritis database. Statistical analysis was performed using Multistat and Statworks software packages. A descriptive analysis was made because the study population was too small for epidemiological techniques such as cluster analysis to be performed. The chi-squared test and Fisher's exact test was used for comparing discrete variables between subgroups, and in evaluating the observed and expected frequencies of nail involvement in relation to adjacent or distant DIP joint involvement. Student's t-test was used for comparing continuous variables for parametric data; the Mann Whitney U test for non-parametric data. Spearman's rank coefficient was used for correlation analysis. Results were deemed significant if $p<0.05$.

# RESULTS

## CLINICAL CHARACTERISTICS

### *Age and Sex Distribution of Psoriasis and Arthritis*

The general characteristics of the study group including the age and sex distribution are given in Table one. Females outnumbered males in this study by 57 to 43 (ratio 1.32:1). The unusual preponderance of females in this series has been discussed in the methods, and may relate to a research interest in the spondyloarthropathies in the same hospital. Sixty-three per cent of patients presented with psoriasis before arthritis, with the remaining patients almost evenly divided between those whose skin disease was discovered incidentally on presentation with arthritis and those who developed skin disease later. Ninety-nine were sero-negative for rheumatoid factor (less than 80 i.u by nephelometry).

### *Mode of Onset and Outcome of Disease Subsets*

The outcome of disease in relation to the mode of onset is summarised in Table 2. Ninety per cent of 39 patients presenting with a monoarthritis, 79% of 24 patients with an oligoarthritis and 20% of 25 patients with a polyarthritis changed pattern. Six of ten patients presenting with spinal symptoms developed a spondyloarthropathy. In total, 64 patients changed pattern, 62 of whom had progression of their disease. Of the four patients who remained in the monoarthritis group three had involvement of one knee and one had disease confined to a single proximal interphalangeal joint. Two patients had apparent regression of their disease with a polyarthritis at onset and subsequently only evidence of an oligoarthritis. Four patients who presented with spinal symptoms developed a peripheral arthritis without spondyloarthropathy. Only one patient, included in the oligoarthritis group, had the synovitis acne pustulosis hyperostosis osteomyelitis syndrome (SAPHO) (Benhamou et al 1988).

The distribution of the site and the type of joint disease at onset are shown in Table 3. Fifty-three patients presented with small joint disease which was more frequent in females ($p< 0.01$) as was upper limb disease at onset ($p<0.05$). Thirty-one of these (24 females, seven males, $p < 0.01$) presented with hand disease which was the most common site of onset . Axial onset was more frequent in males ($p<0.01$) and those presenting with spinal disease were significantly younger (mean age 41.8 years, standard deviation 6.9) than the oligoarthritis (mean 47.9 $^{+}$/-14.7) ($p< 0.05$) or polyarthritis (mean 50.5$^{+}$/- 15.0 years) ($p<0.02$) groups. The mean ages for the monoarthritis and mutilans groups were 48.2 $^{+}$/- 12.1 years and 59.0 $^{+}$/- 16.0 years respectively.

***The relationship of Disease Duration to Functional Outcome and the Use of DMARDs***

Table 4 shows the disease duration, HAQ scores and use of DMARDs of the subgroups. Not unexpectedly, the polyarthritis group had a significantly worse functional outcome defined by HAQ scores than the oligoarticular and monoarthritis groups combined ($p<0.05$). They had also used more disease modifying therapy ($p<0.01$), had a longer disease duration ($p<0.01$), and more erosions ($p<0.001$) than the oligoarticular group. Of those with peripheral arthritis, patients with more severe disease had longer disease durations. Those with arthritis mutilans had the longest disease duration followed by polyarthropathy, with the monoarthritis/DIP joint disease only and oligoarthropathy groups having the shortest disease durations.

Ninety-one patients were taking NSAIDs and 26 disease modifying antirheumatic drugs (DMARDs); a further 14 patients had taken DMARDs in the past. The distribution of the current and previous use of DMARDs is shown in Table 5. Intramuscular gold was most commonly used followed by methotrexate, sulphasalazine, auronofin, penicillamine, azathioprine, hydroxychloroquine. Six patients had also taken prednisolone (4 at the time of study) and one patient

cyclophosphamide. Twenty-eight patients had taken two or more DMARDs and 13 had had surgery for joint disease. Patients taking DMARDs had a significantly longer disease duration (17.2 v 8.8 years, p <0.001) and significantly greater functional disability (p<0.001) than those without.

***Symmetry of Peripheral Joint Disease***

The frequency of symmetry depended on the method employed. When only one identical contralateral joint was required to define symmetry, all 63 of the polyarthritis group and six of 22 of the oligoarthritis group had symmetrical disease. When Helliwell's method was used, 51 of 63 patients in the polyarthritis group and 4 of 22 patients in the oligoarthritis group had symmetrical disease.

***Relationship between Joint Disease and Skin and Nail Involvement***

The distribution of the specific types of skin and nail disease are shown in Table 6. This distribution is similar to that in the general psoriatic population (Camp 1992). There was no association between the type or distribution of skin involvement and arthritis subgroup, nor was there any relationship between the activity of psoriasis and joint severity, activity or functional status. The timing of onset of joint disease in relation to the pattern of onset and ontcome of joint disease is shown in Table 7. However, there was a significant correlation between the number of involved joints (joint score) and functional status (HAQ Score). There was a significant correlation between PASI and the nail scores (p<0.001) and nail disease increased with the duration of psoriasis (p<0.02) (Table 8).

Sixty-seven per cent of patients had psoriatic nail disease, which is a greater frequency than that found in psoriasis alone (c 40%) and reflects that found in previous studies (up to 80% (Roberts et al 1976)). All patients with hyperkeratosis or "dystrophy" had either pitting, onycholysis or both. The nail score was significantly greater in those who developed psoriasis before arthritis or simultaneously (p<0.05).

Nail disease occurred in all subgroups (Table 3). There was no correlation between nail severity and the severity of arthritis. Males tended to have more severe skin and nail disease than females, but this was not significant.

Twenty seven per cent of patients had clinical and/or radiological evidence of DIP joint disease in their hands which is less than reported in other series (Potter and McEwan 1992). Those with DIP joint disease tended to have a longer disease duration than those without (means 15.6 years and 11.0 years respectively) but this was not significant. DIP joint disease occurred in all subgroups except spondyloarthropathy and monoarthritis, but only one patient had DIP joint disease exclusively (Table 3).

Nail disease was more common in patients with DIP joint involvement (85% with DIP joint involvement v 60% without) ($p<0.02$). The association of nail disease and adjacent DIP joint disease was analysed by calculating the observed and expected frequencies of DIP joint disease in relation to adjacent affected and unaffected nails. Fingers and thumbs if the hands were included and the IP joints of the thumbs were considered to be equivalent to the DIP joints of the fingers. For example, a single affected nail on one digit of one hand would have a one in ten chance of association with a single affected DIP joint. Chi-squared and Fisher's exact tests were used, depending on the number of observations. The accumulated data revealed that patients with nail disease in a particular hand were significantly more likely to have DIP disease in this hand than on a hand without nail disease ($p<0.05$). The detailed analysis showed that patients with nail disease in a particular digit were significantly more likely to have DIP joint disease in the adjacent joint than patients without nail disease in that digit (p values for each of the ten digits analysed ranged from $p<0.02$ to $p<0.001$). Accumulating the data for all the digits, DIP joint disease was significantly more likely to occur with nail disease in the adjacent joint than alone ($p<0.01$).

Patients with DIP joint disease also tended to have more severe nail disease, but this did not reach significance.

***Conclusions*** .

To conclude, the pattern of joint disease, defined by joint number changed in sixty-four of the 100 patients studied, i.e. the subgroup of onset did not remain constant with time. Nail disease (67% of total) was more common in patients with DIP joint disease (27% of total), and was significantly associated with adjacent DIP joint disease.

However, the data from this study must be interpretated with an appreciation of its limitations. Fistly, the ascertainment bias has already been discussed in the methods. Secondly, the study was cross-sectional in design and data regarding the pattern of joint disease at onset was retrospective and not subject to a rigorous protocol. Thirdly, the patients had a large range of disease durations, with patients with the longest disease durations developing more extensive disease, hence the application of this data in assessing the prognosis of individual patients within a fixed timescale is limited. Finally, the subgroups were defined by the number of joints involved, which obscures the differing patterns of disease within the polyarticular group. Some of these limitation have been addressed in the prospective follow-up study presented in Chapter 2b.

## TABLE 1

## Clinical Features in 100 Patients with Psoriatic Arthritis

| Clinical Feature | |
|---|---|
| Number of females | 57 |
| Number of males | 43 |
| Mean age (years) (range) | 49.7 (16-80) |
| Mean age at onset of skin lesions (years) (range) | 28.9 (3-70) |
| Mean age of onset of joint disease (years) (range) | 37.6 (5-70) |
| Psoriasis before arthritis | 63 (24M/39F) |
| Simultaneous onset | 20 (12M/8F) |
| Arthritis before psoriasis | 17 (7M/10F) |
| Mean duration of psoriasis (years) (range) | 20.8 (1-61) |
| Mean duration of arthritis (years) (range) | 12.1 (1-53) |
| Family History of psoriasis | 39 |
| Nail Lesions | 67 |
| Iritis | 5 |

**TABLE 2. Evolution of Disease Subsets** The number of patients in each combination of subgroups at onset and at the time of the baseline assessment (outcome) in the psoriatic arthritis clinic is shown. The total number in each group at onset is shown in the final column, and the total for each group at outcome is shown in the final row. The mean age of onset by mode is also shown.

| | | Outcome | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Mode of Onset** | Mean Age of Onset by Mode | Mono | DIP | Oligo | Poly | Spond | Arthritis Mutilans | Total |
| Monoarthritis (Mono) | 37.5 | 4 | 0 | 13 | 22 | 0 | 0 | 39 |
| DIP Joint Disease Only | 41 | 0 | 1 | 1 | 0 | 0 | 0 | 2 |
| Oligoarthropathy (Oligo) | 38.1 | 0 | 0 | 5 | 18 | 0 | 1 | 24 |
| Polyarthropathy (Poly) | 41.1 | 0 | 0 | 2 | 20 | 0 | 3 | 25 |
| Spondyloarthropathy(Spond) | 28.2 | 0 | 0 | 1 | 3 | 6 | 0 | 10 |
| Total | 37.6 | 4 | 1 | 22 | 63 | 6 | 4 | 100 |

## TABLE 3

**Type and Site of Joint Disease at Onset by Sex.** The significance of the difference in the sex distribution for each mode of onset is shown

| Joint Disease | M | F | Significance | Total |
|---|---|---|---|---|
| Small | 18 | 35 | ($p<0.01$) | 53 |
| Large | 12 | 17 | (NS) | 29 |
| Lower Limb | 18 | 24 | (NS) | 42 |
| Upper Limb | 11 | 27 | ($p<0.05$) | 38 |
| Axial | 9 | 1 | ($p<0.01$) | 10 |
| Small and Large | 3 | 4 | (NS) | 7 |
| Small and Axial | 1 | 0 | (NS) | 1 |
| Spinal and Peripheral Disease | 1 | 0 | (NS) | 1 |
| Upper and Lower Limb | 6 | 3 | (NS) | 9 |

**TABLE 4** **Pattern of joint disease by sex, age of onset, disease duration of arthritis and psoriasis, HAQ score, use of DMARDs, and the presence of nail and distal interphalangeal joint disease** Significant differences between subgroups are also indicated at the base of the table.

| Subgroup | No. of Patients | Sex | | Mean age of Onset of Arthritis (Years) | Mean Duration Arthritis (years) | Mean Duration Psoriasis (years) | Mean HAQ Score | Use of DMARD (% Subgroup) | Nail Disease (% Subgroup) | DIP Disease (% Subgroup) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | M | F | | | | | | | |
| Monoarthritis (Mono) | 4 | 1 | 3 | 51 | 6.8 | 24.8 | 0.41 | 0 | 3 (75) | 0 |
| Distal Interphalangeal Joint Disease Only (DIP) | 1 | 1 | 0 | 45 | 10 | 10 | 0.125 | 0 | 1 (100) | 4 (100) |
| Olgoarthropathy (Oligo) | 22 | 8 | 14 | 41.3 | 6.6 | 14.5 | 0.49 | 9.1 | 13 (59) | 3 (9) |
| Polyarthropathy (Poly) | 63 | 25 | 38 | 36.6 | 13.9 | 20.2 | 0.87 | 50.8 | 45 (71) | 19 (30) |
| Spondyloarthropathy (Spond) | 6 | 6 | 0 | 29.2 | 13.7 | 19.5 | 0.65 | 33 | 2 (33) | 0 |
| Arthritis Mutilans (AM) | 4 | 1 | 3 | 32.5 | 21.5 | 30 | 1.34 | 75 | 3 (75) | 4 (100) |
| Total | 100 | 43 | 57 | 37.6 | 12.5 | 20.6 | 0.77 | 40 | 67 | 27 |

**Subgroup Comparisons**

Duration of Psoriatic Arthritis: poly v oligo (t test), $p=0.007$; oligo v spond, $p=0.038$

HAQ Score: poly v oligo + mono (t test), $p<0.05$;

Use of DMARDs: poly v oligo (chi-squared test), $p<0.01$

## TABLE 5

**Distribution of Therapy** The number of patients on each medication when first seen in the psoriatic arthritis clinic (baseline) and since onset (previous) is shown. The cumulative number of patients on each medication is shown in the first column.

| Therapy | Number of Patients | Baseline | Previous |
|---|---|---|---|
| NSAIDS | 91 | 91 | 0 |
| All DMARDs | 40 | 26 | 14 |
| Intramuscular Gold | 19 | 9 | 10 |
| Methotrexate | 13 | 8 | 5 |
| Sulphasalazine | 11 | 5 | 6 |
| Penicillamine | 7 | 1 | 6 |
| Azathioprine | 7 | 1 | 6 |
| Hydroxychloroquine | 4 | 4 | 0 |
| Oral Steroids (for joint disease) | 6 | 4 | 2 |
| Cyclosporin | 2 | 1 | 1 |
| Surgery | 13 | NA | NA |

## TABLE 6

**Pattern of Psoriasis and Nail Disease** The percentage of patients with a particular type of psoriasis and nail disease is shown.

| Type of Psoriasis (%) | | Type of Nail Disease (%) | |
|---|---|---|---|
| Plaque | 79 | Pitting | 74 |
| Scalp | 70 | Onycholysis | 70 |
| Discoid | 10 | Hyperkeratosis | 34 |
| Guttate | 4 | Severe nail deformity ("dystrophy") | 5 |
| Pustular | 3 | | |

## TABLE 7. Onset of skin disease in relation to onset of arthritis by the pattern of joint disease at onset and at the baseline assessment in the clinic (outcome)

| | | Mode of Onset | | | | | Outcome | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Total (M/F) | Mono | DIP | Oligo | Poly | Spond | Mono | DIP | Oligo | Poly | Spond | Arthritis Mutilans |
| **Psoriasis before Arthritis** | 63 (24/39) | 27 | 1 | 13 | 18 | 4 | 2 | 0 | 16 | 39 | 4 | 2 |
| **Simultaneous Onset** | 20 (12/8) | 2 | 1 | 8 | 5 | 4 | 1 | 1 | 2 | 14 | 1 | 1 |
| **Arthritis before Psoriasis** | 17 (7/10) | 10 | 0 | 3 | 2 | 2 | 1 | 0 | 4 | 10 | 1 | 1 |
| **Total** | 100 (43/57) | 39 | 2 | 24 | 25 | 10 | 4 | 1 | 22 | 63 | 6 | 4 |

**TABLE 8.**

**Joint, Skin and Nail Correlations** The significance of correlations between joint damage and activity, skin, nail and HAQ scores are shown.

| Parameters | Spearman Correlation Coefficient | Significance |
|---|---|---|
| Jt Score v HAQ | 0.458 | <0.001 |
| Jt Score v Nail Score | 0.12 | NS |
| Jt Score v PASI | -0.029 | NS |
| Jt Score v Jt Activity | -0.033 | NS |
| HAQ v Nail Score | -0.103 | NS |
| HAQ v PASI | -0.022 | NS |
| PASI v Nail | 0.361 | <0.001 |
| PASI v Active Jts | 0.053 | NS |
| Nail v Active Jts | 0.131 | NS |
| HAQ v Active Jts | -0.046 | NS |
| Nail Score v Duration Psoriasis | 0.26 | 0.013 |

# DISCUSSION

Attempts to classify psoriatic arthritis have been complicated by the overlap between subgroups, the importance given to extraosseus abnormalities, including the synovitis-acne-pustulosis-hyperostosis-osteomyelitis syndrome (SAPHO) (Benhamou et al 1988), the definition of symmetry, the relationship of DIP joint disease to the subgroups and the temporal change in the pattern of arthritis.

Moll and Wright, based on their own descriptive work (Wright 1956, Wright 1959, Wright 1961, Wright and Moll 1971) and radiological studies by Avila et al (Avila et al 1960) described five clinical patterns: (i) "classic" psoriatic arthritis confined to DIP joints of hands and feet (5%); (ii) arthritis mutilans with sacro-ileitis (5%); (iii) symmetric polyarthritis, indistinguishable from rheumatoid arthritis (15%); (iv) asymmetric oligoarthritis (70%); and (v) spondylo-arthropathy (5%)(24). Further studies and review articles reaffirmed these subgroups (Wright and Moll 1976, Moll and Wright 1973, Moll 1979, Little et al 1975, Leonard et al 1978, Molin 1978, Scarpa et al 1984, Moll 1984), although the overlap between subgroups and possible evolution from one subgroup to another was noted (McCormack and Barth 1985). A more recent study using radionucleotide scanning concluded that all patients with peripheral arthritis should be grouped together, the spondyloarthropathy group retained and a new group added, comprising rare patients with extra-articular osseous disease, including patients with SAPHO (Helliwell 1991). Applying this classification to our patients, 94 were grouped together, 6 remained in the spondylarthritis group and only one belonged to the extraarticular osseous group. Radionucleotide scanning may have revealed more patients with extra-articular osseous abnormalities, but this is not practical in a clinical setting. Whilst the extra-articular osseus group including SAPHO should be recognised, its relative rarity makes its separate classification difficult to justify, a point also made by Veale et al (1994). Other attempts at reclassification include that by Gladman et al (1986), who

initially increased the number of groups to seven, but later in a review of 220 patients, proposed a spectrum of disease patterns and severity (Gladman et al 1987). Most recently three groups have been suggested (Veale et al 1994), similar to those proposed by Kammer (Kammer et al 1979), with the spondyloarthropathy group retained and peripheral arthritis divided into two subgroups - asymmetric arthritis and symmetric polyarthritis. The groups are loosely defined in terms of the assessment of symmetry and the number of joints involved, but the classification may prove useful clinically.

I divided our patients into six subgroups - monoarthritis, DIP joint disease alone, oligoarthritis, polyarthritis, spondyloarthritis and arthritis mutilans. The three patients with monoarthritis would be included in Moll and Wright's asymmetrical oligoarticular subgroup, but the lack of progression of disease beyond one knee and the absence of DIP disease distinguished them from the rest of the subgroups. The mean disease duration for the monoarthritis subgroup was similar to that of the oligoarthritis subgroup but about half of the mean for all patients, so it is possible that the patients in these subgroups may have progression of their disease and change subgroup. It is striking that, for those with peripheral arthritis, those with more extensive and severe joint involvement (arthritis mutilans and polyarthropathy groups) had longer disease durations than the DIP joints disease only, oligoarthritis and monoarthritis groups. This raises the possibility that the number of joints involved is a function of disease duration. The homogeneity of the spondyloarthropathy group in this study, with all six patients presenting with spinal symptoms and the absence of DIP joint disease, supports the view that this subgroup should be retained (Helliwell et al 1991, Veale et al 1994).

The number of patients with oligoarthritis, which tends to be asymmetrical, and polyarthritis, which tends to be symmetrical, has varied considerably between studies largely because of differences in subgroup definitions. The subgroup

frequencies initially reported by Moll and Wright, who found a majority of patients (70%) in the asymmetrical oligoarticular group only 15% in the symmetric polyarthritis group (Moll and Wright 1973) has not been confirmed in other series. In our study, the ratio of oligoarthritis (including monoarthritis patients to make studies comparable) to polyarthritis was 1 to 2.3. Gladman et al, in a study of 220 patients, also found that oligoarthritis was far less common than polyarthritis with a ratio of 1: 2.2 (Gladman et al 1986 and 1987) and the preponderance of patients with polyarthritis has subsequently been confirmed by Wright et al, when a more rigid definition of the number of joints involved was used (Wright 1992). However, in a recent study of 100 patients, Veale et al (1994) clearly illustrate the difficulties in classifying the peripheral arthropathy of psoriatic arthritis by the use of two methods of classifying their patients. The text states that they found the asymmetrical oligoarthritis subgroup more common than symmetrical polyarthritis with a ratio of 1.3:1, although 11 patients with an asymmetrical polyarthritis were included in the oligoarticular group. They then applied strict definitions of symmetry and number of joints involved, as used by Helliwell et al (1991), and found 45% of patients in the asymmetrical oligoarticular group, 11% in an asymmetrical polyarticular group and 38% in the symmetrical polyarticular group. When these patients were included in the polyarthritis group, the ratio of polyarthritis to oligoarthritis of 1.1 to 1.0. Therefore, once again patients with polyarthritis outnumbered those with oligoarthritis.

The use of both the number of joints involved and symmetry to define the oligoarticular and polyarticular subgroups has proved difficult in other series (Kammer et al 1979, Barraclough et al 1977). Obviously, the fewer joints involved, the more likely the disease is to be asymmetrical but a small number of patients will inevitably have a symmetrical oligoarthritis or an asymmetrical polyarthritis. The difficulty is illustrated by the differing results of the two methods employed in this study and we therefore did not use symmetry to define our subgroups.

The rarity of pure DIP joint involvement and its occurrence over the spectrum of disease patterns has been previously noted (Green et al 1981, Laurent 1985, Veale et al 1994, Torre Alonso et al 1991). In our series DIP joint disease occurred in all subgroups except spinal disease and the monoarthritis group, and three patients had DIP joint involvement exclusively. The association of DIP joint disease with nail disease in the same digit has long been recognised (Bauer et al, 1941), although detailed analysis has not been performed. This study confirms that there is a topographical association of nail disease with DIP joint disease when analysed for each digit and for each hand.

The evolution of disease patterns from the oligoarthritis to the polyarthritis group is a further matter of debate. Whereas Gladman has suggested that this is common (Gladman 1992c), Helliwell et al (1991) found that only 5% changed pattern. In the current study, 64% of patients presenting with monoarticular or oligoarticular disease developed polyarthritis. These patients may have changed pattern early in the course of their disease before reaching a plateau, although the significantly greater disease duration for the polyarthritis group suggests that the number of joints involved is a function of disease duration. To conclude, the subgroup of onset did not remain constant with time, i.e. the mode of onset did not predict outcome in the majority of patients, and hypothesis (i) was disproven. This is further studied in the prospective 5 year follow-up study of Chapter 2b.

Although the attempts to define clinical subgroups of joint disease have added greatly to our clinical perception of psoriatic arthritis, it has had limited impact on our understanding of the pathogenesis. The lack of any serological markers for the disease, adds to this difficulty. In addition, there are no clearcut HLA associations related to specific subgroups of joint or skin disease, although the association of the class II antigens HLA DR to peripheral disease and HLA-DR4 with erosive

disease requires further elucidation (McHugh et al 1987, Chapter 2c). The association of nail disease and DIP joint disease is possibly the only clinical evidence that there is a peripheral biological link between events in the skin and the joint. Research into disease mechanisms at a genetic and cellular level is needed to elucidate the true relationship between psoriatic skin, nail and joint disease (Chapters 2c and d; Chapter 3)

***Conclusions***

To conclude, the major findings from this study are that the subgroup of onset did not remain constant with time, i.e. the mode of onset did not predict outcome in the majority of patients. Hypothesis (i) (see list of hypotheses and study aims and summary at the beginning of this chapter) is therefore disproven. The subgroup of disease is at least in part a function of disease duration. This finding is likely to apply to other classification systems in which the number of involved joints is used to define subgroups.

This is the first which statistically analyses the association between nail and adjacent DIP joint disease, although the observation was originally made by others earlier this century (Bauer, 1941, Wright 1956). The topographic association of nail and adjacent DIP joint disease provides clinical evidence for a local inflammatory mechanism that may link the two manifestations of the disease.

## CHAPTER 2b

# PROGRESSION OF PERIPHERAL JOINT DISEASE IN PSORIATIC ARTHRITIS: A FIVE YEAR CLINICAL AND RADIOLOGICAL FOLLOW-UP STUDY

## SUMMARY

***Introduction.*** The progression of disease in psoriatic arthritis, the homogeneity of disease subgroups, and predictive factors for disease progression have been infrequently studied. ***Hypothesis.*** Psoriatic arthritis is a progressive disease, with increasing joint involvement in the majority. ***Study Aim.*** To perform a prospective clinical and radiological follow-up study of the patients included in Chapter 2a.

***Study Design.*** Prospective.

***Methods*** . The 100 patients described in Chapter 2a were followed up after a median of five years. Nine patients had died and five were unavailable for follow-up. A further patient on whom complete data was available was included. In total 87 (49 females, 38 males) completed the proforma detailed in Chapter 2a. Seventy-five patients had serial hand radiographs scored using a modified Sharp's Index. A bivariate analysis of initial factors versus rates of progression of joint and HAQ scores was performed.

***Results*** . The clinical subgroups were as follows (cross-sectional study /follow up study): monoarthritis 4/1; DIP joint disease only 1/1; oligoarthritis 23/11, polyarthritis 51/59, mutilans 2/3 and predominant spondylitis 6/7. Five patients (2 previously monoarthritis and 3 oligoarthritis) had no clinical evidence of joint involvement at follow-up. In total, 19 patients changed subgroup, 12 had an increase in the number of joints involved, six a decrease, and one changed from an oligoarticular pattern to predominant spondylitis. Within the polyarticular group 37/51 patients had an increase in the number of joints involved. Four patients with predominant spondyloarthropathy also had peripheral joint disease. For the whole population, there were significant increases in the number of joints involved (median

6 v 11, $p<0.001$ Wilcoxon signed rank), erosion and joint space narrowing scores in the hands and HAQ scores (median 0.375 v 0.5, $p<0.001$). There were no significant differences in skin and nail scores although 9 further patients had developed nail disease. There was a significant correlation between the initial viscosity and rate of progression of joint damage (Spearman correlation, $p<0.011$).

***Conclusions***. This study provides evidence that peripheral joint disease in psoriatic arthritis is progressive in the majority of patients and reinforces the need for effective monitoring and treatment.

# INTRODUCTION

The natural history of psoriatic arthritis, the homogeneity of disease subgroups, and predictive factors for disease progression have been infrequently studied (Gladman 1994 and Gladman et al 1995b). A cross-sectional study of the first 100 patients to attend the psoriatic arthritis clinic in Bath is presented in Chapter 2a and has been published (Jones et al 1994) . One of the major conclusions of this study was that the mode of onset did not predict outcome in the majority of patients. Forty patients progressed from a monoarticular or oligoarticular pattern of disease at onset to develop polyarthritis. However, the study had a number of limitations, which are described in the concluding paragraph of the discussion to Chapter 2a. Of particular importance are the ascertainment bias. cross-sectional and retrospective design and variable disease durations between disease onset and baseline evaluation. Some of these limitations have been addressed in the current prospective study which describes the clinical distribution of joints involvement and assesses progression within a fixed timescale.

Data on the pattern and rate of progression of radiological changes in the hands in patients with psoriatic arthritis is also limited (Roberts et al 1976, Gladman et al 1990). Furthermore there is no data on the prevalence of distinctive radiographic features such as bony proliferation, DIP involvement, periostitis, joint space widening, bony ankylosis, osteolysis and tuftal changes in a cohort of patients. It has been previously reported that radiographic damage tends to occur early in the course of psoriatic arthritis and then reaches a plateau, although few studies have addressed this prospectively (Gladman et al 1990). The progression of radiological changes in the hands and the relationship between parameters of radiological severity and clinical joint scores is addressed in the current study.

A prospective study of 87 psoriatic arthritis patients is now presented at a median follow-up interval of 65 months. The primary aims were to determine the clinical progression of peripheral joint disease, to further evaluate subgroup homogeneity, and to determine possible predictors for disease progression. The secondary aims were to determine and quantify the pattern and progression of radiological features in the hands and to relate the progression of radiographic joint damage to clinical parameters. The cross-sectional study (Chapter 2a) revealed no significant associations between the activity or severity of joint disease and the activity and severity of psoriasis or nail disease, but demonstrated a statistically significant topographic association between nail and DIP disease. This has been further evaluated in the current study. Hence, the third aim was to assess the evolution of skin and nail disease and its relationship to joint disease.

# PATIENTS AND METHODS

***Patients***

Eighty six patients (48 females and 38 males) from the cross-sectional study (Chapter 2a) were available for follow-up and one additional patient (a female) on whom there was complete initial data was included, so the total number of patients was 87. A possible reason for the excess of females has been discussed in Chapter 2a. Patients were followed at a median of 65 months (range 39 - 90). Fifty of these 87 patients were still attending the psoriatic arthritis clinic or other general rheumatology clinics in Bath; the remaining thirty-seven patients were contacted by letter or telephone and asked to attend a follow-up appointment. Of the remaining 14 patients, nine had died, two could not be traced and three declined follow-up; two of the latter were elderly, lived outside the region and were unable to travel; a further patient declined follow-up, preferring to attend practitioners of alternative medicine. The cause of death of the nine patients who died was ascertained by obtaining the contemporary medical records or general practitioner's notes; where these were incomplete or unhelpful, the general practitioner was contacted by telephone.

***Demographic Data and Joint Involvement***

A proforma identical to that completed in the cross-sectional study was completed on all patients. This included a standardised examination of peripheral joint and axial involvement, skin psoriasis score using the PASI index, nail score
(Appendix A) and functional assessment using a HAQ Score. Patients were divided into subgroups based on objective evidence of involvement on examination at follow-up. The subgroup distinctions employed in the cross sectional study were used as follows:- monoarthritis ; DIP joint disease only; oligoarthritis (<5 joints involved), polyarthritis (>4 joints involved), arthritis mutilans and predominant spondylitis. Arthritis mutilans was defined as a severe deforming polyarthritis causing widespread radiographic osteolysis and the 'opera glass' hand. The

peripheral joint score ranged from 0 - 70 joints involved with one point scored for each involved joint. The joints included were DIP joints, IP joints of the thumbs, PIP joints, MCP joints, wrists, elbows, shoulders, temporo-mandibular, sterno-clavicular and acromio-clavicular, hips, knees, ankles (mortice joint), talocalcaneal, midtarsal, metatarsal-phalangeal joints, inter-phalangeal joint of the first toe and the remaining toes. The spine was excluded from this score although involvement of the cervical and lumbar spine was noted. A full blood count, rheumatoid factor and inflammatory markers including a viscosity, ESR and C-reactive protein were obtained.

***Hand Radiology***

Standard antero-posterior views of the hands were also performed with verbal consent, irrespective of hand symptoms or signs. The films were single emulsion on a mammographic plate. Ethical approval was obtained from the Bath and South West Ethical Committee

Seventy five pairs of films taken at baseline and follow-up were subsequently available for assessment (median interval 65 months, range 39 - 90). The scorer was blinded to the clinical details of the patients and the order at which the radiographs were taken. At least ten sets of radiographs were scored at one single reading by the same observer. A modified Sharp's index was used to score the radiographs, which has been validated in the course of this study. A full description of the index and its modification is included in Appendix B. Briefly, the index scores the number and severity of erosions and joint space narrowing; the latter was modified for psoriatic arthritis and termed joint space abnormality to included apparent widening of the joint space.

The pattern of involvement and other radiological features of interest which have been reported as being characteristic of psoriatic arthritis were also documented.

The following signs have been reported as differentiating psoriatic arthritis from rheumatoid arthritis:- phalangeal tufts, osteolysis, bony proliferation, periostitis, asymmetry, apparent joint space widening and bony ankylosis. Juxta-articular osteopenia, soft tissue swelling, DIP and wrist involvement were also noted and malalignment was graded as moderate (subluxation) or severe (dislocation).

***Data Analysis***

All data was stored in a Microsoft Excel database and analysed using Statworks and Multistat software packages on an Apple Macintosh Computer. The distribution of the various data sets was assessed first and a descriptive comparison of the data at baseline and follow up was made initially. A bivariate analysis of initial factors versus rates of progression of joint HAQ and radiographic data was performed. Correlations between data sets were assessed using Spearman's non-parametric method.

***Skin and Nails***

The skin and nails were examined using a pre-defined protocol under the supervision of a dermatologist. The PASI and Nail Scores were computed, as in Chapter 2a (Appendix A)

# RESULTS

### *Demographic Data and Mortality*

The demographic data for the 87 patients is shown in Table 1. Nine patients had died since the original study. Five of the deaths were related to coronary artery disease, but one death was attributed to immobility and general debility associated with psoriatic arthritis mutilans. All of the patients who died were elderly.

### *Evolution of Joint Disease and Functional Outcome*

The evolution of clinical subgroups used in Chapter 2a (Jones et al 1994) is shown in Table 2. In total, 19 patients (22%) changed pattern, 12 of whom had an increase in the number of joints involved, six had decreased joint involvement, one had no change in symptoms, and a further patient who initially had peripheral joint involvement with four joints involved developed predominant spondyloarthritis. One patient with polyarthritis evolved to arthritis mutilans. The number of joints involved in the patients with polyarthritis at baseline increased in 37 out of 51 patients. Joint involvement in the patients with polyarthritis at baseline increased in 37 out of 51 patients. Four patients with predominant spondyloarthropathy also developed peripheral joint disease. Four patients (two with monoarthritis at baseline and two with oligoarthritis at baseline) had no clinical evidence of joint disease, although one of these had mild dactylitis of the toes. One male patient continued to have evidence of distal joint disease exclusively.

The distribution of joint involvement in the 87 patients at baseline and follow-up is shown in Tables 3 and 4.

For the whole group, the number of joints involved increased (median 6 v 11, $p < 0.001$). .The HAQ scores also increased (median 0.375 v 0.5, $p < 0.001$).

***Extra-articular Features and Laboratory Parameters***

One female (disease duration 40 years) developed cervical myelopathy secondary to a combination of psoriatic and osteoarthritic lower cervical spine disease. She presented insidiously with neck pain and a slowly evolving quadriplegia and made an excellent recovery from surgical decompression and stabilization. Prior to the development of the myelopathy, this patient was included in the paper describing cervical spine disease in this cohort of patients (Jenkinson et al 1994).

Only one patient was sero-positive for rheumatoid factor at baseline, but a further three further patients had become rheumatoid factor positive by follow-up (titre >1/80 by nephelemetry), all of whom had polyarthritis. Plasma viscosities were available for all patients at baseline and follow-up. ESR and C-reactive protein were only measured on all patients at follow-up. Fifty patients (57%) had elevated plasma viscosities at baseline compared with 45 (52%) patients at follow-up. However, the mean plasma viscosity at follow-up was greater than at baseline (1.77 versus 1.67, not significant). Only 20 patients at follow-up had C-reactive protein levels greater than 10 mg/l, the lower limit of estimation in our laboratory.

***Hand Radiology***

The cumulative scores for erosions and joint space abnormalities (see Appendix B) at baseline and at follow-up increased for all joints except for the joint space abnormality score for the proximal interphalangeal joint of the right hand (Table 5). (This may reflect the inclusion of joint space widening in the joint space abnormality score. For example, one patient with mutilating disease had radiographic ankylosis (score 4) followed by a reappearance of the joint space (score 0), although the latter represented an extension of the pathological process and should possibly have been scored as 4 for joint space widening). Both erosion and joint space abnormality scores were greatest at the wrist at both baseline and follow up. Of the finger joints, distal interphalangeal joints tended to be less affected in terms of erosions or joint

space abnormalities than the proximal interphalangeal joints, which were most severely affected, or the metacarpo-phalangeal joints. The percentage increase in cumulative joint scores was greater for erosions than joint space abnormalities (59% v 35.5%).

Forty patients had erosions at baseline. Of these, 26 had more erosions, nine remained stable and five showed healing. Nine additional patients had developed erosions at follow-up. Thirty-eight patients had joint space abnormalities at baseline and 30 of these deteriorated, five remained stable and three improved. A further 11 patients had developed joint space abnormalities at follow-up. The median erosion scores at follow-up were significantly greater than at baseline (0.0665 (range 0 - 2.6) versus 0.02190 (range 0 - 2.13), $p < 0.01$. The median rate of progression of erosions (change in erosion score per month) was 0.00195 (range 0.00014 - 0.033). Joint space abnormality scores were also significantly greater at follow up than at baseline (median 0.185 (range 0 - 3.24) versus 0.046 (range 0 - 3.52), $p < 0.001$ Wilcoxon signed rank). The median rate of progression of joint space abnormality was 0.00089 (range 0.01 - 0.038).

Figure one shows the prevalence of the reported characteristic features of psoriatic arthritis at baseline and follow-up. All these features increased apart from tuftal changes, which decreased. Radiographic evidence of distal-interphalangeal joint disease increased and was present at follow-up in over one third of patients.

***Evolution of Nail and Skin Disease***

There were no significant differences between skin and nail scores at baseline and follow-up. The types of psoriasis did not change between baseline and follow-up and there was no association between subgroups of skin disease or type of psoriasis or severity of psoriasis based on the PASI score. Eleven further patients had developed nail disease, so a total of 68/87 (78%) had nail disease. Twenty-three of the eighty-

seven patients reported simultaneous exacerbations of their skin and peripheral joint disease. The temporal relationship between joint, skin and nail disease has been studied prospectively in a cohort of twenty-four patients in Chapter 2c.

***Correlations between Clinical and Radiographic Parameters and Predictive Factors for Disease Progression***

There were significant positive correlations between the baseline erosion and joint space abnormality scores and the duration of arthritis ($p<0.001$ for both, Spearman correlation). Baseline clinical joint scores positively correlated with the rates of progression of erosions and joint space narrowing (Spearman, $p < 0.001$). Baseline erosion and joint space abnormality scores correlated with the rates of progression of erosions and joint space abnormalities respectively (Spearman, $p < 0.001$), implying that those with more severe disease at baseline had a greater capacity to undergo progressive joint damage.

There was an insignificant negative correlation between disease duration at baseline and the rates of progression of joint scores and erosions suggesting that the rates of progression may slow slightly with time. However, there was a slight positive trend in correlation between the rate of progression of joint space abnormality and disease duration, possibly reflecting the increase in incidence of osteoarthritis with time.

There was also a significant correlation between initial viscosity and the rate of progression of joint damage (Spearman, $p<0.011$).

***Conclusions***. In total, 19 patients changed subgroup, 12 had an increase in the number of joints involved, six a decrease, and one changed from an oligoarticular pattern to predominant spondylitis. The majority of patients within the polyarticular group (37/51) had an increase in the number of joints involved. Four patients with predominant spondyloarthropathy also developed peripheral joint disease. For the

whole population, there were significant increases in the number of joints involved erosion and joint space narrowing scores in the hands and HAQ scores. There were no significant differences in skin and nail scores although 9 further patients had developed nail disease. There was a significant correlation between the initial viscosity and rate of progression of joint damage, which may be a predictive factor for disease progression.

# TABLE 1. Demographic Data and Mortality

| | | |
|---|---|---|
| No of patients followed up | | 87 |
| No. of patients lost to follow-up | | 5 |
| No. of deaths | | 9 |
| Median age of death (range) | | 70.5 (63 - 83) |
| Causes of death | | |
| | cardiac disease | 5 |
| | bronchopneumonia and a perforated gastric ulcer | 1 |
| | carcinoma of the breast | 1 |
| | psoriatic arthritis mutilans | 1 |
| | unknown | 1 |
| Sex (female: male) | | 49:38 |
| Median age in years (range) | | 53.5 (21 - 85) |
| Median disease duration at follow-up in years(range) | | 15.5 (5 - 58) |
| Median follow-up time in months (range) | | 65 (39 - 90) |

**TABLE 2. Evolution of disease subsets from baseline to follow-up (N=87)** The rows and columns show the numbers of each combination of subgroups at baseline and follow-up. The final column shows the total number and percentage of patients in each subgroup at baseline, and the final row shows the total number and percentage of patients in each subgorup at follow-up.

| | Subgroup at Follow-up | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Subgroup at Baseline** | **Mono** | **DIP** | **Oligo** | **Poly** | **Spond** | **Arthritis Mutilans** | **Nil** | **Total in subgroup at baseline (% of total patients)** |
| **Nil** | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| **Monoarthritis (Mono)** | 1 | 0 | 0 | 0 | 0 | 0 | 3 | 4 (4.6) |
| **DIP Joint Disease Only** | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 (1.1) |
| **Oligoarthropathy (Oligo)** | 1 | 0 | 10 | 10 | 1 | 0 | 2 | 23 (26.4) |
| **Polyarthropathy (Poly)** | 0 | 0 | 1 | 49 | 0 | 1 | 0 | 51 (58.6) |
| **Spondyloarthropathy(Spond)** | 0 | 0 | 0 | 0 | 6 | 0 | 0 | 6 (6.9) |
| **Arthritis Mutilans** | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 2 (2.3) |
| **Total in subgroup at follow-up (% of total patients)** | 1 (1.1) | 1 (1.1) | 11 (12.6) | 59 (67.8) | 7 (8.0) | 3 (3.4) | 5 (5.7) | 87 (100) |

**TABLE 3. Clinical distribution of joint involvement in the small joint of the hands and feet at baseline and follow-up.** The number of patients with involvement of a particular joint is shown and the percentage increase in involvement from baseline to follow-up is indicated for both right and left sides

| | Right | Right | % Increase From Baseline | Left | Left | % Increase From Baseline |
|---|---|---|---|---|---|---|
| **HAND** | | | | | | |
| **MCPs (total)** | **39** | **45** | **15** | **27** | **39** | **44** |
| MCP1 | 23 | 31 | **35** | 23 | 34 | **48** |
| MCP2 | 22 | 35 | **59** | 18 | 30 | **67** |
| MCP3 | 19 | 31 | **63** | 18 | 28 | **56** |
| MCP4 | 9 | 22 | **144** | 6 | 18 | **200** |
| MCP5 | 10 | 22 | **120** | 8 | 20 | **150** |
| **PIPs (total)** | **30** | **43** | **43** | **30** | **39** | **30** |
| IP(Thumb) | 17 | 26 | **53** | 15 | 23 | **53** |
| PIP2 | 14 | 26 | **86** | 16 | 25 | **56** |
| PIP3 | 19 | 27 | **42** | 19 | 29 | **53** |
| PIP4 | 9 | 21 | **133** | 12 | 25 | **108** |
| PIP5 | 10 | 23 | **130** | 11 | 24 | **118** |
| **DIPs (total)** | **19** | **34** | **79** | **18** | **31** | **72** |
| DIP2 | 14 | 22 | **57** | 12 | 24 | **100** |
| DIP3 | 14 | 23 | **64** | 14 | 22 | **57** |
| DIP4 | 7 | 19 | **171** | 10 | 21 | **110** |
| DIP5 | 9 | 23 | **156** | 10 | 18 | **80** |
| **Hand (total)** | **51** | **58** | **14** | **52** | **60** | **15** |
| **FEET** | | | | | | |
| **MTP Joints** | | | | | | |
| MTP1 | 23 | 38 | **65** | 23 | 35 | **52** |
| MTP2 | 27 | 35 | **30** | 26 | 30 | **15** |
| MTP3 | 32 | 37 | **16** | 29 | 32 | **10** |
| MTP4 | 25 | 29 | **16** | 22 | 28 | **27** |
| MTP5 | 20 | 29 | **45** | 22 | 28 | **27** |
| **Toes** | | | | | | |
| IP1 | 19 | 23 | **21** | 15 | 24 | **60** |
| Toe2 | 17 | 28 | **65** | 22 | 31 | **41** |
| Toe3 | 15 | 26 | **73** | 19 | 28 | **47** |
| Toe4 | 18 | 28 | **56** | 14 | 25 | **79** |
| Toe5 | 13 | 23 | **77** | 14 | 24 | **71** |

**TABLE 4. Clinical distribution of joint involvement in the large joints, temporo-mandibular, sterno-clavicular and acromio-clavicular joints at baseline and follow-up.** The number of patients with involvement of a particular joint is shown and the percentage increase in the baseline number of patients from baseline to follow-up is indicated for both right and left sides.

| | Right | Right | % Increase | Left | Left | % Increase |
|---|---|---|---|---|---|---|
| Temporo-mandibular | 1 | 2 | 100 | 0 | 2 | NA |
| Sterno-clavicular | 0 | 2 | NA | 0 | 4 | NA |
| Acromio-clavicular | 0 | 1 | NA | 0 | 2 | NA |
| Shoulder | 12 | 27 | 125 | 15 | 28 | 87 |
| Elbow | 13 | 16 | 23 | 13 | 20 | 54 |
| Wrist | 13 | 16 | 23 | 13 | 20 | 54 |
| Hip | 5 | 11 | 120 | 2 | 8 | 300 |
| Knee | 22 | 31 | 41 | 28 | 29 | 4 |
| Ankle | 6 | 20 | 233 | 6 | 17 | 183 |
| Talocalcaneal | 11 | 14 | 27 | 12 | 12 | 0 |
| Midtarsal | 2 | 5 | 150 | 0 | 4 | NA |

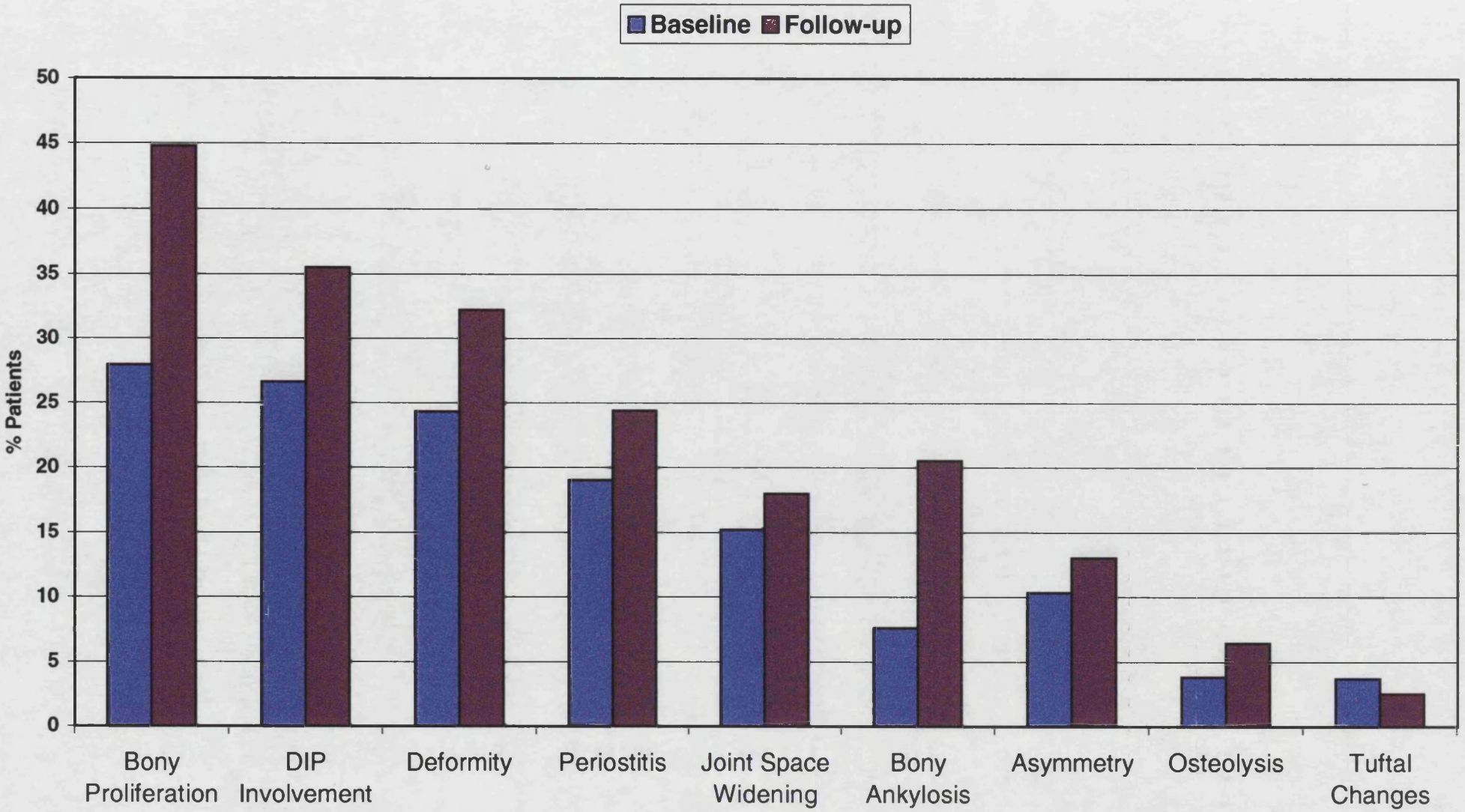
NA - not applicable because no involvement at baseline

**TABLE 5. Total scores for erosions (ERO) and joint space abnormalities (JSA) for the joints of the hands and wrists at baseline and follow-up in 75 patients** Left and right hands are shown separately an d the percentage increase in the scores from baseline to follow-up is indicated. All the scores increased except for the JSA score for the PIP joints of the right hand, which decreased, possibly reflected the inclusion of joint space widening in the scoring system.

| | Left hand | | | | | | Right hand | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Joints** | **ERO** (baseline) | **ERO** (follow-up) | **% Increase** | **JSA** (baseline) | **JSA** (follow-up) | **% Increase** | **ERO** (baseline) | **ERO** (follow-up) | **% Increase** | **JSA** (baseline) | **JSA** (follow-up) | **% Increase** |
| **DIP** | 107 | 148 | **38** | 123 | 177 | **44** | 94 | 142 | **51** | 103 | 140 | **36** |
| **PIP** | 124 | 216 | **74** | 168 | 178 | **6** | 130 | 191 | **47** | 169 | 154 | **-9** |
| **MCP** | 98 | 164 | **67** | 121 | 224 | **85** | 139 | 214 | **54** | 146 | 254 | **74** |
| **CMC** | 68 | 115 | **69** | 112 | 167 | **49** | 78 | 107 | **37** | 153 | 233 | **52** |
| **Carpal** | 151 | 274 | **81** | 199 | 252 | **27** | 157 | 271 | **73** | 219 | 281 | **28** |
| **Rc+Ru** | 56 | 88 | **57** | 59 | 69 | **17** | 59 | 75 | **27** | 59 | 84 | **42** |
| **Total** | **604** | **1005** | **66** | **782** | **1064** | **36** | **657** | **849** | **29** | **849** | **1146** | **35** |

Rc = radio-carpal
Rc = radio-ulnar

**FIGURE 1. Distribution of radiological features of psoriatic arthritis at baseline and follow-up**



# DISCUSSION

### *Mortality in Psoriatic Arthritis*

There have been few studies of mortality in psoriatic arthritis. The data from the study by Roberts et al (1976) is similar to the current study. In this study 168 patients were followed up from 1 to 10 years. There were 18 deaths, nine of which were from complications of atherosclerosis, 3 from infections, 2 from malignancies, 2 from haemorrhages and 2 were unknown. One patient died under the age of 50 with a myocardial infarction. Brubaker et al (1992) had 20 deaths in a follow-up study of 304 patients over 11 years, none of which were directly attributed to psoriatic arthritis. The studies and numbers of deaths are all too small to make definite conclusions.

The largest mortality has recently been published (Wong et al 1997). This study evaluated the causes of deaths and standardised mortality ratios (SMR) of 53 deaths in patients attending a single out-patient clinic in Canada. There was a significantly increased mortality compared with the general population in both men and women (SMR 1.65 and 1.59 respectively). The proportions of the various causes of death were similar to that in the general population, with the exception of respiratory disease which was increased, although no cause could be identified. Thirty-six per cent of deaths were from circulatory causes; although this was slightly greater than occurred in the general population, it did not reach statistical significance. Psoriatic arthritis was considered a contributory factor in only one death, as in the current study.

### *Evolution of Joint Disease*

To date, there have been few studies in which patients with psoriatic arthritis have been assessed over a period. Roberts et al (1976) reported that 94 of 168 patients with psoriatic arthritis had been followed for more than 10 years, 15 for 5 - 10

years, 32 for 2-4 years and 15 were seen once. Their follow-up suggested that patients who presented with a distal arthritis often proceeded to have multiple joints involved. Those who presented with a polyarthritis or deforming arthritis continued to further deteriorate, with data similar to our study. The percentage who deteriorated was less than in our study, possibly reflecting the diverse range of follow-up times.

This prospective follow-up study further emphasizes the preponderance of polyarthritis in established disease which tends to be symmetrical, as opposed to the asymmetry of mono or oligoarthritis. This progression of joint involvement has been reported in the small number of previous prospective studies (Gladman et al 1994 and 1995b). In the current study, the percentage of patients with oligoarthritis based on involvement of five or less joints was only 13.7% at follow-up, closer to the figure from a study from Southern Italy (Della Valle et al), than studies from the United Kingdom or the USA (Moll and Wright 1973, Bennett 1985).

Only one patient in our series continued to have distal joints involved exclusively. This has not been found as an exclusive feature of arthritis in some series (Kammer et al 1979, Torre Alonso 1991, Helliwell et al 1991) but has been found exclusively in others (Gladman et al 1987). The presence of exclusive distal interphalangeal (DIP) joint disease has been debated (Helliwell and Wright 1992, Scarpa et al 1992, Veale and Fitzgerald 1992) and the presence of isolated DIP joint disease remains controversial. Only four patients from the original cohort of 100 developed arthritis mutilans, one of whom died prior to the follow-up study, confirming the rarity of this condition even in hospital attendees with psoriatic arthritis.

Hanly et al (1988) assessed 52 patients with psoriatic spondyloarthritis over 30 months and showed that, whereas there was no clinical evidence of a significant increase in spinal disease, peripheral joint disease progressed. However, neck disease

is a common feature of psoriatic arthritis (Jenkinson et al 1994) and caused cervical myelopathy in one patient. This complication is recognised in psoriatic arthritis and has been recently reported (Agaki et al 1996).

It has been recognised that some patients may have a benign cause with an initial presentation which subsides never to recur. Gladman has also reported complete resolution in 7 patients. This was the case in 4% of our patients , who had no evidence of joint involvement at follow-up. However one of these had non-tender mild dactylitis of the toes, which is interesting in the light of the recent suggestion that enthesopathy and dactylitis may represent a separate subgroup of joint disease (Salvarani et al 1997)

In general, psoriatic arthritis has been considered to be a milder form of arthritis than rheumatoid arthritis. The pattern of involvement of the small joints of the hands is similar to rheumatoid arthritis. Even when the distribution of joint involvement and synovitis is similar, patients with psoriatic arthritis may appear to have less pain and disability than rheumatoid arthritis (Oriente 1994). This may be related in part to the characteristic lack of joint tenderness in psoriatic arthritis compared with rheumatoid arthritis (Buskila et al 1992). Charcot's joints have recently been reported in association with arthritis mutilans. The lack of joint tenderness may result in underestimating the extent of the disease, so it is important to review appropriate radiographs. Some patients with radiographic joint abnormalities may not be appreciated clinically in routine circumstances. This is a critical part of the evaluation and may influence therapeutic decisions.

Scarpa et al (1989) described 57 patients with psoriatic arthritis treated with auronofin. At 12 months there was improvement in the inflammatory activity in 64% of patients. However, there was no clinical information after 12 months, or radiological data to support the statement that psoriatic arthritis is a mild articular

disease. Gladman et al (1995b) assessed patients who had been followed up prospectively for at least five years. There was clear evidence of alleviation of joint inflammation. However more patients developed both clinical and radiological evidence of damage, as in the current study. It was noted in Gladman's study that the rate of progression of joint damage at follow-up was lower than at the initial visit, indicating that more damage occurred early in the course of disease.

***Functional Assessment***

The HAQ has been validated in rheumatoid arthritis and modified for use in spondyloarthritis (Daltry et al 1990). It has been recently modified to include limitations due to skin disease (Husted et al 1995). In the current study, which focused on peripheral joint disease, and used objective measures of skin involvement, we have used the standard HAQ, so that the data directly measures peripheral joint dysfunction and can be compared with studies of rheumatoid arthritis.

The HAQ socre deteriorated with time (median 0.35 to 0.5), but much less than has been found in studies of rheumatoid arthritis. In a study of 1,274 patients with rheumatoid arthritis, 50% had a HAQ score of >1 at 2 years, 50% had a HAQ score of > 2 at six years and 50% had a HAQ score of > 2.5 at 10 years (Wolfe and Cathay 1991; Wolfe et al, 1991). Gladman found the HAQ to correlate with pain and fibrositic tender points rather than joint damage. The low HAQ scores are consistent with the low joint tenderness observed in the disease (Buskila et al 1992).

***Laboratory Features***

IgM rheumatoid factor was positive in one patient at baseline and follow up and a further three patients at follow-up. In a previous long-term follow-up study, 16% of 131 PsA patients were consistently sero-positive and 10% fluctuated between positive and negative results (Roberts et al 1976).

Gladman et al (1995) assessed patients who had been followed up prospectively for at least five years. There was a clear evidence of alleviation of joint inflammation demonstrated by a reduction in the number of actively inflamed joints and a reduction in the ESR. This was accompanied by higher use of non-steroidal anti-imflammatory drugs and disease-modifying anti-rheumatic drugs at the follow-up visit. Despite the fact that inflammation appeared to subside, deformity and damage progressed, suggesting, perhaps, that treatment may not have been provided early enough in the course of the diseases. In the current study, a high initial viscosity at baseline is associated with a greater rate of progression of clinical joint involvement and may be a predictive factor for its progression. This has also been shown by Gladman (Gladman et al, 1995).

***Hand Radiology***

Erosive disease in the hands was common. In our population, which were not selected on the basis of hand symptoms, 46% had erosions at baseline which increased to 56% at follow-up. Nissila et al (1983) followed 14 patients with psoriatic arthritis for at least three years. The number of patients with erosive disease increased from 8 to 11, although the number with inflamed joints reduced. The authors concluded that patients with psoriatic arthritis had a similar progression to rheumatoid arthritis. Hence radiological damage in the hand is progressive in the majority of patients with psoriatic arthritis, especially those with widespread damage at baseline.

The prevalence of the specific radiographic features or psoriatic arthritis increase with time but overall are present in a minority of patients. A comparison between polyarticular psoriatic arthritis and disease duration-matched, gender-matched controls with rheumatoid arthritis and osteoarthritis would be useful to determine

differences in the pattern and severity of damage and the specificity of the reported features of psoriatic arthritis.

One of the largest percentage increases in the specific features of psoriatic arthritis is in bony ankylosis, which may cause particular disability in the hand (Gladman et al 1990), particularly when it affects the wrist or MCP joints, rather than the distal joints. Fibrosis precedes ankylosis, which may be related to the release of specific cytokines. Loosening of the joint due to the pencil-in-cup deformity also increased although it remained uncommon. It is also a disabling deformity, even if isolated to distal joints, because of their importance in fine movement such as unbuttoning a shirt.

***Skin and Nail Involvement***

There was a remarkable similarity in the PASI and nail scores at baseline and follow-up. Nail disease has been consistently found to be increased in patients with psoriatic arthritis versus those with psoriasis alone (Camp 1992). It is on interest that eleven further patients had evidence of nail disease at follow-up, with a total percentage of 78%.

***Conclusions***

Psoriatic arthritis is a heterogeneous disease in onset, expression and outcome. The arthritis may vary considerably in its pattern and has been divided into several subgroups (Moll and Wright 1973, Chapters 2a). This current study provides evidence that psoriatic arthritis is not the benign disease once considered; polyarthritis is most common in patients referred to rheumatologists (Wright 1992, Jones et al 1994), and the majority of patients have progressive peripheral joint disease. This is consistent with Gladman's work, based on the largest existing database of psoriatic arthritis (Gladman et al 1995b). However, it must be remembered that there are a small number of patients (five in this study, seven

reported by Gladman (Gladman 1994) who have isolated or infrequent episodes of joint inflammation and who do not develop clinical evidence of joint damage. In the current study radiological damage in the hand was also progressive, especially those with widespread damage at baseline. Hence overall the study provides evidence that peripheral joint disease in psoriatic arthritis is progressive in the majority of patients and reinforces the need for effective monitoring and treatment.

However, the unpredictability of the course of peripheral disease and response to therapy is of major concern to both patient and rheumatologist. Good prognostic indicators are essential in justifying early intervention. The strongest known clinical prognostic indicator to date is the inflammatory marker – the viscosity was measured in the current study, and the ESR in Gladman' s work (Gladman et al 1995a) both of which are associated with an increase rate of progression of disease.

## CHAPTER 2c

# THE TEMPORAL RELATIONSHIP BETWEEN JOINT, SKIN AND NAIL DISEASE - A PROSPECTIVE 2 YEAR STUDY

## SUMMARY

***Introduction.*** It has been estimated from cross-sectional work that the activity of skin and peripheral joint disease in psoriatic arthritis may fluctuate concurrently in one quarter to one third of patients (Chapter 2b, Gladman 1987).

***Hypothesis.*** Patients with simultaneous exacerbations or remissions of skin and joint disease may represent a distinct subset of psoriatic arthritis.

***Study Design.*** Prospective.

***Methods***. Twenty-four patients with psoriatic arthritis were evaluated for the severity and activity of skin, nail and joint disease at approximately three monthly intervals over a minimum period of two years. All patients had peripheral joint involvement and evidence of active joint disease at baseline.

***Results.*** Twelve patients considered that they had periodic exacerbations of joint and skin activity at baseline, but this was not substantiated by prospective study. Only four patients always had simultaneous flares or remissions of skin and joint disease and a further nine sometimes had simultaneous flares or remissions; the remaining eleven patents had no relationship between skin or joint exacerbations or an inverse relationship. The four patients in whom simultaneous flares or remissions occurred throughout the study and the nine patients in whom simultaneous flares or remissions sometimes occurred were not distinguished by any specific feature of their joint disease.

***Conclusions*** . Simultaneous flares or remissions of peripheral joint and skin disease occur invariably in a minority of patients with psoriatic arthritis. This

characteristic is independent of the timing of onset of joint disease in relation to skin disease and does not define a distinct subset of joint disease.

# INTRODUCTION

Clinical descriptive and epidemiological studies have conclusively established a link between psoriasis, nail disease and arthritis. However, the precise relationship between these three manifestations of the disease remains uncertain. It has also been reported that psoriasis tends to be more severe in patients with psoriatic arthritis and nail disease tends to be more common, although this data has been disputed (Camp 1992). It is unclear whether the severity of skin disease may be an independent prognostic factor for psoriatic arthritis. Some individuals, 20% in most studies, present with joint symptoms before skin lesions appear whereas, in the majority, up to 80%, skin problems manifest themselves first. It would therefore appear that a separate triggering event is required for the initiation of the three manifestations of disease. Once these three manifestations are established, the temporal relationship between the activity and severity of joint disease and the activity and extent of skin disease and nail disease may be important to patients and rheumatologists in determining disability and in devising treatment strategies. This has never previously been assessed prospectively.

Gladman reported that 35% of patients have simultaneous exacerbations of skin and peripheral joint disease (Gladman et al 1987), but no relationship was reported by patients with predominant spondyloarthropathy. The data was not obtained prospectively, although the figure has often been quoted in reviews (Gladman 1994). In Chapter 2b, 23 of 87 patients (26.4%) reported simultaneous exacerbations of skin and joint disease. Hence, it is possible that there may be a subset of patients with psoriatic arthritis, distinguished by simultaneous exacerbations of their disease that share a common immunogenetic profile.

The aim of the current study was to prospectively evaluate the temporal association of skin and joint involvement. The frequency of simultaneous exacerbations of

joint, skin and nail disease was assessed in patients attending the psoriatic arthritis clinic who had active skin and joint disease at baseline.

# PATIENTS AND METHODS

### *Patients*

Patients attending the psoriatic arthritis clinic in Bath were recruited for the study. Patients were entered into the study based on the following criteria - established psoriatic arthritis and stable medication for joint and skin disease at baseline. All patients verbally consented to the study and committed themselves to attending eight further appointments at approximately three monthly intervals over a minimum of two years. Recruitment occurred over a nine month period and a total of 29 patients entered the study, 5 of whom were withdrawn because of missing data after baseline (e.g. failure to keep the study appointment; inflammatory markers not available). Data was accumulated using a specially designed form.

### *Methods*

All patients were seen by the same investigator (SJ) at approximately three monthly intervals. Data was entered on the psoriatic arthritis database after each clinic visit. At the baseline visit, information was taken including a detailed history of skin joint and nail disease using the proforma described in Chapters 2a and b. Patients completed a self-assessment questionnaire at baseline which included a question about simultaneous exacerbations of skin and joint disease. The joints, skin and nails were examined at each assessment. The activity of a joint disease was assessed using a modified Ritchie index for tender joints and a joint swelling score (Eular 1993; Appendix C). The pattern and number of joints involved was also evaluated by counting the number of active and damaged joints, so that the subgroup of joint disease could be determined. Functional assessment was made using the modified Stanford Health Assessment Questionnaire disability index (Kirwan et al 1986). A skin (PASI score) and nail scoring system was used to assess the severity and extent of skin and nail disease using methods previously described (Appendix A). At each visit changes to the medication for joint or skin disease, other interventions such as

inpatient therapy for psoriasis, PUVA, UVB, joint injections, or admissions for skin or joint disease were noted. Radiological examination was performed where clinically indicated. All patients were managed according to guidelines established in the psoriatic arthritis clinic.

Haematological and biochemical markers of disease severity including a full blood count and differential, erythrocyte sedimentation rate, C-reactive protein and plasma viscosity were taken at each visit. The ESR, CRP and viscosity are all process markers of activity of joint disease activity, but not skin psoriasis (Brahn and Scoville 1988; Sitton et al 1987, Laurent et al 1981, Oriente et al 1984). A rheumatoid factor was performed at the baseline assessment.

The ESR, modified Ritchie index and joint swelling score were used to calculate a modified disease activity score which has been validated in rheumatoid arthritis and early synovitis (Eular, 1993; Appendix C). Global assessment of disease activity was not used as this may be influenced by the activity of psoriasis. The ESR was preferred to the CRP and viscosity because it has been validated for use in this index, there was no missing data after baseline in any patient, and because it covers the full range. The laboratory minimum for the CRP is 10mg/l, although it is recognised that values below this may be abnormal.

***Descriptive Analysis.***

Joint. skin and nail scores were entered onto an Excel database and plotted so that the tendency for joint, skin or nail scores to change simultaneously or otherwise from one time-point to the next could be readily described. The data graphs for each patient are shown in Appendix D. Exacerbations or remissions or joint and skin disease, joint and nail disease and nail and skin disease were deemed to have an equal chance of occurring simultaneously or inversely. To determine whether

exacerbations or remissions of the three manifestations of disease occur sequentially, the data for each patient was plotted on a grid.

# RESULTS

***Baseline Data***

The demographic data for the patients included in this study is shown in Table 1. By chance more women were recruited, reflecting both the slight sex predominance in the clinic and the greater commitment of the women to attend follow-up appointments. All patients were sero-negative for rheumatoid factor. Only ten patients (40%) had the rheumatoid arthritis 'shared epitope', which is less than the percentages found in control populations (Chapter 2d) and reflects the fact that our population was sero-negative for rheumatoid factor and distinct from rheumatoid arthritis. Twelve patients were taking either sulphasalazine or methotrexate at baseline.

Nineteen patients developed psoriasis before arthritis, in three patients psoriasis was discovered when the arthritis presented, and in six the arthritis presented first. The duration of nail disease was not remembered reliably in most patients so the data is not included. Nine patients said that they had simultaneous flares of their joint and skin disease on questioning at baseline.

Sixteen of the twenty-four patients had nail disease at baseline and a further five patients (numbers 3, 5, 8, 18, 19 and 23) developed nail disease during the course of the study. Two further patients developed nail disease after the study was completed (patients 7 and 23).

The scores for joint, skin and nail disease for all twenty-four patients have been plotted and are shown for each patient in Appendix D. The tendency for simultaneous flares or remissions of joint, skin and nail disease to occur is summarised in Table 2, and plotted for skin and joint disease, joint and nail disease and nail and skin disease in Figures 1a to c.

*Temporal Relationship of Joint and Skin Disease*

Only five patients always had simultaneous flares or remissions of skin and joint disease and a further nine sometimes had simultaneous flares or remissions; the remaining ten patents had no relationship between skin or joint exacerbations or an inverse relationship (Table 2). The tendency for simultaneous flares or remissions was unrelated to patient perception of a relationship at baseline. Of the nine patients who considered that they had periodic exacerbations of joint and skin activity at baseline, simultaneous flares or remissions occurred in only five, with no consistent relationship or an inverse relationship in the remaining four patients. In total, joint and skin disease flared simultaneously in 61% of 117 episodes in which significant changes in both joint and skin scored occurred, with an inverse relationship in the remaining 40%, which is only slightly more that would be expected by chance. The thirteen patients in whom simultaneous exacerbations or remissions occurred were not distinguished by the timing of onset of arthritis in relation to psoriasis or any other features of their joint or skin disease.

No consistent time-lag between exacerbations or remissions of skin and joint disease was observed.

*Temporal Relationship of Joint and Nail Disease*

Three patients had simultaneous flares of joint and nail disease, a further six tended to have simultaneous flares; five had no tendency, eight had a tendency for an inverse relationship and two always had an inverse relationship (Table 2). In total, joint and nail disease flared simultaneously in only 35 of 75 time-points in which significant changes in joint and skin scores occurred; at the remaining 40 time-points the changes were in opposite directions.

No consistent time-lag between exacerbations or remissions of skin and joint disease was observed.

***Temporal Relationship of Nail and Skin Disease***

Four patients had simultaneous flares of skin and nail disease, a further six had simultaneous flares most of the time; in seven there appeared to be no relationship, in five there was a tendency for an inverse relationship and in two there was always an inverse relationship. In total, nail and skin disease flared simultaneously at 38 of 61 time-points in which significant changes in both nail and skin scores occurred, with an inverse relationship at the remaining 23 time-points.

No consistent time-lag between exacerbations or remissions of skin and joint disease was observed.

***Effect of Treatment***

The possible effects of modification of treatment for either skin or joint disease are complex, and the analysis in this study has been performed using the raw data without speculating on the possible differential confounding effect of treatment. Examples of possible effects are as follows. In patient three sulphasalazine was stopped and then restarted between time-point 6 and 7 (Appendix D), coinciding with a flare and remission of both joint and skin disease; the same pattern was seen in patient 17 between time-points one and 2 (Appendix D); in patient 7, UVB was given prior to appointment 7 - and improvement in the PASI score was noted and the joint score also improved (Appendix D); in patient 5 the dose of methotrexate was increased from 12.5mg per week to 15mg per week between appointments four and five coinciding with an improvement in the joint score, but not the PASI score (Appendix D).

*Conclusions*

In summary, 12 patients considered that they had periodic exacerbations of joint and skin activity at baseline, but this was not substantiated by prospective study. Only four patients always had simultaneous flares or remissions of skin and joint disease and a further nine sometimes had simultaneous flares or remissions; the remaining eleven patents had no relationship between skin or joint exacerbations or an inverse relationship. The four patients in whom simultaneous flares or remissions occurred throughout the study and the nine patients in whom simultaneous flares or remissions sometimes occurred were not distinguished by any specific feature of their joint disease.

Hence, simultaneous flares or remissions of peripheral joint and skin disease occur invariably in a minority of patients with psoriatic arthritis. This characteristic is independent of the timing of onset of joint disease in relation to skin disease and does not define a distinct subset of joint disease.

**TABLE 1. Baseline characteristics of the 24 patients** The patients are numbered as in Table 2 and Appendix D.

| Patient Number | Age | Duration Psoriasis | Duration Arthritis | Age Psoriasis | Age Arthritis | Family History | Subgroup Arthritis | Pattern of Psoriasis | Nail Disease | DIP Joint Disease | Effusions | Dactylitis | Spondylitis | Erosions | Use of DMARDS | Shared Epitope |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 54 | 36 | 24 | 18 | 30 | y | SP | P | y | y | n | n | y | y | y | y |
| 2 | 36 | 23 | 16 | 13 | 20 | n | AO | PS | y | n | n | y | n | n | n | y |
| 3 | 29 | 6 | 5 | 23 | 24 | y | AO | PS | n | y | n | y | n | y | y | n |
| 4 | 34 | 13 | 5 | 13 | 29 | n | SP | PS | y | y | n | n | n | y | n | n |
| 5 | 21 | 5 | 5 | 16 | 16 | y | AP | PS | n | y | y | y | n | y | y | n |
| 6 | 54 | 42 | 4 | 12 | 50 | y | SP | P | y | y | y | y | n | y | n | y |
| 7 | 30 | 8 | 5 | 22 | 5 | n | SP | PS | y | n | y | n | y | n | y | y |
| 8 | 62 | 10 | 17 | 53 | 45 | y | SP | PSG | n | n | y | n | n | n | y | n |
| 9 | 33 | 9 | 5 | 24 | 28 | y | AO | NIL | y | n | n | y | n | n | n | n |
| 10 | 39 | 9 | 8 | 30 | 31 | n | AO | PS | y | n | y | n | y | n | y | n |
| 11 | 28 | 7 | 2 | 21 | 26 | n | SP | P | y | n | y | y | n | y | n | n |
| 12 | 57 | 9 | 5 | 48 | 52 | n | AO | GS | y | y | n | y | n | n | n | y |
| 13 | 30 | 4 | 3 | 26 | 27 | n | AO | PS | y | y | n | y | n | n | n | y |
| 14 | 31 | 13 | 4 | 18 | 27 | y | SP | PS | y | y | n | n | n | y | y | n |
| 15 | 47 | 11 | 5 | 35 | 41 | n | AO | P | n | n | n | n | n | n | n | y |
| 16 | 32 | 25 | 16 | 7 | 16 | y | AP | S | y | y | n | y | n | y | n | y |
| 17 | 19 | 6 | 4 | 13 | 15 | y | AO | PS | y | y | y | n | n | n | y | y |
| 18 | 47 | 41 | 6 | 6 | 41 | n | SP | PS | n | y | n | n | n | n | n | y |
| 19 | 40 | 14 | 10 | 20 | 24 | y | SP | PGS | n | y | n | y | n | y | y | n |
| 20 | 38 | 16 | 16 | 22 | 22 | y | SP | Nil | y | y | n | n | n | y | n | n |
| 21 | 40 | 20 | 17 | 20 | 23 | n | AO | PS | y | y | n | n | n | n | n | n |
| 22 | 48 | 0 | 1 | 47 | 46 | n | AP | P | n | y | n | y | n | n | y | n |
| 23 | 25 | 1 | 1 | 24 | 24 | n | AO | PG | n | y | y | y | n | n | y | n |
| 24 | 62 | 12 | 5 | 50 | 57 | y | SP | PGS | y | y | n | n | n | y | y | n |
| **Mean or Total** | **39** | **14.2** | **7.8** | **24.2** | **30** | **12** | **NA** | **NA** | **16** | **17** | **8** | **12** | **3** | **11** | **12** | **10** |

AO = asymmetrical oligoarthritis
SP = symmetrical polyarthritis

P = plaque psoriasis; G = guttate psoriasis; S = scalp psoriasis

## TABLE 2. The temporal relationship between joint, skin and nail disease.

| Patient Number | Simultaneous Flares or Remissions of Joint and Skin Disease | Patients Reporting Simultaneous Flares of Joint and Skin Disease | Simultaneous Flares or Remissions of Joint and Nail Disease | Simultaneous Flares or Remissions of Skin and Nail Disease |
|---|---|---|---|---|
| 1 | Always | Yes | Inverse relationship always | Inverse relationship always |
| 2 | Sometimes | Yes | Inverse relationship sometimes | Inverse relationship sometimes |
| 3 | Sometimes | No | Inverse relationship sometimes | Sometimes |
| 4 | Inverse relationship always | No | No relationship | Sometimes |
| 5 | No relationship | Yes | Always | No relationship |
| 6 | Sometimes | No | Sometimes | Always |
| 7 | Always | No | No relationship | No relationship |
| 8 | Sometimes | No | Always | Always |
| 9 | No relationship | No | Always | No relationship |
| 10 | Inverse relationship sometimes | Yes | No relationship | Sometimes |
| 11 | Sometimes | No | Inverse relationship sometimes | Inverse relationship sometimes |
| 12 | Inverse relationship sometimes | Yes | Inverse relationship sometimes | Sometimes |
| 13 | Sometimes | Yes | Inverse relationship sometimes | Inverse relationship sometimes |
| 14 | Sometimes | No | Sometimes | Sometimes |
| 15 | No relationship | Yes | No relationship | No relationship |
| 16 | Always | Yes | Inverse relationship sometimes | No relationship |
| 17 | Always | Yes | Sometimes | Sometimes |
| 18 | Inverse relationship sometimes | No | Sometimes | Inverse relationship sometimes |
| 19 | Inverse relationship sometimes | No | Inverse relationship sometimes | Always |
| 20 | Inverse relationship sometimes | No | Inverse relationship sometimes | Inverse relationship always |
| 21 | Always | No | Sometimes | Always |
| 22 | Sometimes | No | No relationship | No relationship |
| 23 | Inverse relationship sometimes | No | Inverse relationship always | Inverse relationship sometimes |
| 24 | Sometimes | No | Sometimes | No relationship |

**FIGURE 1a. The temporal relationship between joint and skin disease in 24 patients over 2 years.**

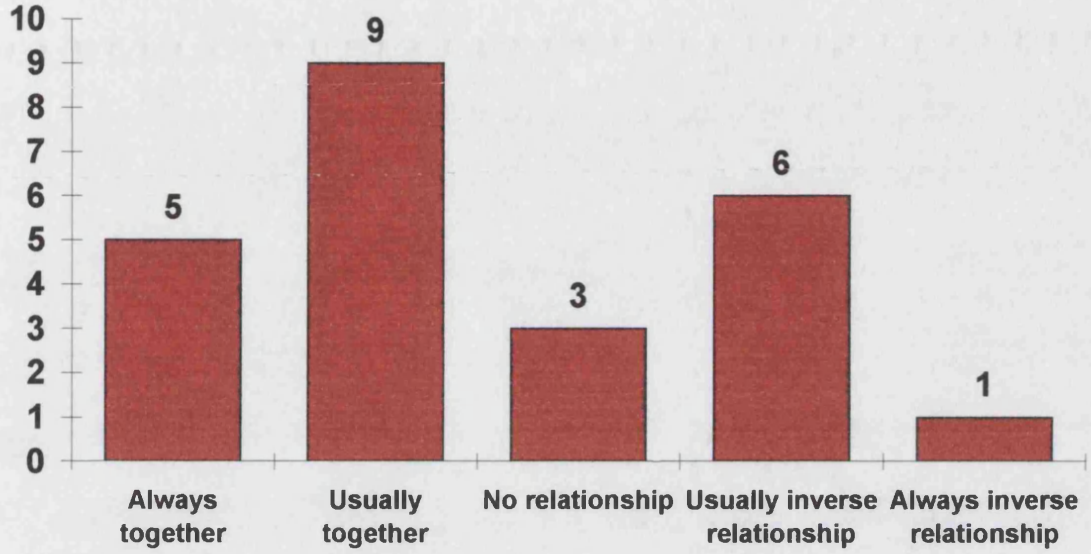



**FIGURE 1b. The temporal relationship between joint and nail disease in 24 patients over 2 years.**

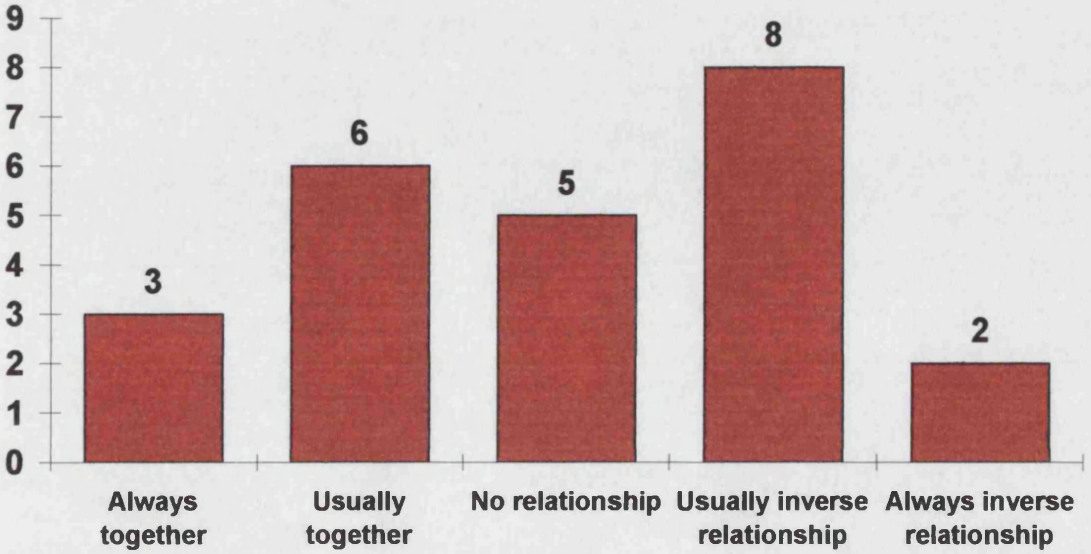
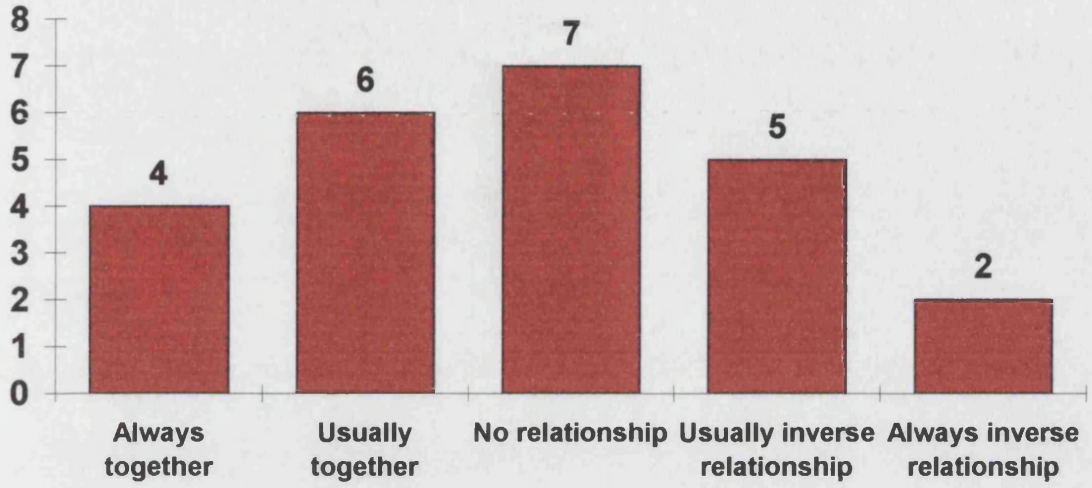


**FIGURE 1c. The temporal relationship between skin and nail disease in 24 patients over 2 years.**



## DISCUSSION

The patients included in this study were typical psoriatic arthritis patients. It is of note that the majority of patients had nail disease (87% by the end of the study) and half the patients had dactylitis at baseline. Nail lesions remain the only clinical feature that identifies patients with psoriasis that are at risk of developing arthritis (Gladman et al, 1986) and evidence from the prospective follow-up study (Chapter 2b) and the current study indicates that this characteristic increases with time.

The absolute scores obtained for skin activity and severity and joint activity also require some discussion. It has been suggested that patients with severe psoriasis tend to develop arthritis and that their arthritis may be more severe, although the evidence for this is flawed (Little et al 1975; Leonard et al 1978). A higher frequency of arthritis has been reported among hospital inpatients with psoriasis; these patients have severe psoriasis necessitating admission, and their arthritis is more likely to be noticed that the general population with psoriasis. In the current study the severity of psoriasis never reached a psoriasis area and severity index (PASI) score of 20, so was remarkably mild; however, some patients received treatment for their psoriasis between appointments which may have influenced the PASI scores and indeed the periodicity of skin activity compared with joint activity. It has been previously noted that the joints of patients with psoriatic arthritis are less tender that those with rheumatoid arthritis (Buskila et al 1992), both over tender fibrositic points and over actively inflamed joints. This may cause difficulty when measuring the extent of the arthritis, and may account for the low modified Ritchie

scores recorded in this study on patients who had clear evidence of joint activity and progression.

Previous cross-sectional data has suggested that there is a clear relationship between a flare in skin disease and peripheral joint disease in approximately one third of patients (Gladman et al 1986). This data was quoted in a later review, where it was acknowledged that it was not obtained prospectively (Gladman 1994). In Chapter 2b, the prospective follow-up study, 23 of 87 patients claimed to have simultaneous exacerbations of their skin and joint disease, and in the current study, nine patients claimed to have simultaneous exacerbations at baseline. However, this was not substantiated by prospective study. Cross-sectional data, based on patient perception, is likely to be unreliable because it is dependent on the most recent recall of the patient, which will by chance include simultaneous exacerbations or remissions in approximately a third of cases.

In all large series of psoriatic arthritis, including my own, some patients have developed arthritis before the appearance of skin lesions (Roberts et al 1976, Kammer et al 1979, Gladman et al 1987. Torre Alonso et al 1991, Chapter 2a; Jones et al 1994), some develop arthritis and psoriasis simultaneously and in the majority psoriasis develops first. A temporal relationship may be considered to be more likely in those who develop the manifestations simultaneously, but the three patients in whom this occurred had an inverse relationship between skin and joint activity.

***Conclusions***

The current study is unique. The activity of joint, skin and nail disease has never

been previously documented prospectively by a single observer. It may represent a window of opportunitity to do the work, because the increasing use of cyclosporin and combination therapies in psoriatic arthritis may obscure the true temporal relationship between the manifestations of disease.

To conclude, in patients with psoriatic arthritis managed by standard therapies in the clinic, concurrent flares of skin and joint disease occur consistently in only a minority of patients. This finding is in keeping with other well-known clinical features of psoriatic arthritis - the arthritis may follow psoriasis by many years or vice-versa and severe arthritis may be accompanied by mild psoriasis or vice-versa. Whether the severity of skin disease is increased overall in patients with arthritis remains uncertain. There are also distinct differences in the cellular immunology of the skin and joints (Barker 1994, Panayi 1994). Although some features of immune dysregulation may be shared by both skin and synovium, other features such as the surface markers of the T lymphocyte populations differ (see Chapter 3). Both manifestations of the disease may respond to methotrexate, cyclosporin and possibly, sulphasalazine, but these non-specific immuno-suppressive agents are used to treat immunologically-mediated conditions affecting many systems (Cuéllar et al 1994, Abu-shakra et al 1995, Clegg et al 1996, Goupille and Valat 1996, Mahle et al 1996, Griffiths 1996). Their mechanisms of action are diverse, and do not in themselves provide evidence of a close relationship between skin and joint disease. However, when individuals do notice a relationship between their skin and joint flares, and in particular when both manifestations of the disease are troublesome, it is sensible to choose a therapeutic agent or combinations of agents with evidence of efficacy in both joint and skin disease.

## CHAPTER 2d

# PREVALENCE OF THE RHEUMATOID ARTHRITIS HLA DRB1 "SHARED EPITOPE" IN 76 PATIENTS WITH PSORIATIC ARTHRITIS

## SUMMARY

***Introduction*** Genetic factors may influence susceptibility and severity in psoriatic arthritis. An epitope encoded by the third, hypervariable region of the DRB1 gene is a major susceptibility factor for rheumatoid arthritis. Nevertheless its association with peripheral disease in psoriatic arthritis has not been determined.

***Hypothesis.*** The rheumatoid arthritis 'shared epitope' may influence susceptibility for and severity of psoriatic arthritis, and may have implications for its pathogenesis.

***Study Aim.*** To determine the prevalence of the 'shared epitope' in patients followed prospectively for 5 years (Chapters 2a and b) and its relationship to clinical subgroups, erosive disease and disease progression.

***Methods*** HLA DRB1 alleles and HLA DR1 and DR4 subtypes were determined by PCR-SSO and PCR-SSP respectively in 76 patients with psoriatic arthritis and 104 normal healthy blood doners. Clinical data was collected on all psoriatic arthritis patients including disease subgroup, joint scores and presence of erosions on hand radiographs.

***Results*** The prevalence of the 'shared epitope' in patients and controls was similar and equal in all subgroups (35/ 76 patients versus 51/104 controls). The "shared epitope" was distributed within subgroups at follow-up as follows (number with epitope/ number in subgroup): distal interphalangeal joint disease only 1/1 ; oligoarthritis 7/15 ; polyarthritis 21/49; predominant spondylitis 4/7; arthritis mutilans 1/3. There was no significant association between the presence of the 'shared epitope' and erosions in the hands, or on the rate of progression of joint

scores or erosions. The *0401 subtype was significantly reduced in psoriatic arthritis patients compared with controls.

***Conclusions*** The 'shared epitope' is present in psoriatic arthritis in a similar proportion to the general population and is present in all subgroups of the disease. The *0401 subtype is under-represented in psoriatic arthritis compared with controls, underlining the different aetiopathogenesis of psoriatic arthritis and rheumatoid arthritis.

# INTRODUCTION

It has been established for over 20 years that certain HLA DR4 and DR1 serotypes are associated with the presence of rheumatoid arthritis in different populations. The further definition of DR4 and DR1 subtypes and the discovery that not all subtypes are associated with rheumatoid arthritis has lead to the'shared epitope hypothesis' (Gregarson 1987). This provides an explanation for the population association between rheumatoid arthritis and difference serologically-defined class II antigens at teh DR locus on the basis of the shared possession of a short sequence of amino acids in the third, hypervariable region of the DRB1 gene. In rheumatoid arthritis, several authors have reported a hierarchy of disease susceptibility with a more pronounced association with 0401 (Dw4) and 0404 (Dw14). Also there is good evidence that HLA-DR4 is associated with disease severity, with increased representation in hospital RA (van Zeben 1991). Homozygosity for the 'shared epitope' or compound heterozygosity, in which two different alleles containing the 'shared epitope' has been found to be linked to severe erosive disease (McDonagh et al 1997).

Genetic susceptibility is likely to be of major importance in the development of psoriatic arthritis. The associations of the MHC Class I molecules are well established. B13, B17, B27 and Cw6 occur with increased frequency in both psoriasis and psoriatic arthritis (Al-Jarallah et al 1993, Eastmond and Woodrow 1977 and Eastmond 1994) and HLA B16 and its splits B38 and B39 are associated with psoriatic arthritis (McHugh et al 1987, Gladman et al 1995a). In psoriasis it has been established that HLA Cw6 is the primary association and that the other HLA Class 1 associations are in linkage disequilibrium with this (Green et al 1988). Of the HLA Class II molecules, DR7 has been found consistently to be increased in both psoriasis and psoriatic arthritis (Armstrong et al 1983, McHugh et al 1987, Gladman et al 1995a). In psoriatic arthritis DR4 has been found to be associated with

peripheral arthritis resembling rheumatoid arthritis by some (Gerber et al 1982, Gladman et al 1986) but not others (Salvarani et al 1989). It has also been associated with erosive disease (McHugh et al 1987). DR1 has also been found to be increased in some studies (Armstrong et al 1983). All these studies used immunocytotoxicity techniques; they did not examine the 'shared epitope' itself.

Psoriatic arthritis is a heterogeneous disease in onset, expression and outcome. The arthritis may vary considerably in its pattern and has been divided into several subgroups (Moll and Wright 1973, Chapters 2a and b). It is not the benign disease once considered; polyarthritis is most common in patients referred to rheumatologists (Jones et al 1994) and significant number of patients have progressive joint disease (Gladman 1995a, Chapter 2b). The unpredictability of the course of peripheral disease and response to therapy is of major concern to both patient and rheumatologist. Good prognostic indicators would be useful in justifying early intervention.

The objectives of this study were therefore to (i) determine to prevalence of HLA DRB1 alleles and the 'shared epitope' in hospital outpatients with psoriatic arthritis compared with healthy controls; and (ii) to determine the association of the "shared epitope" with subgroups of disease and erosive disease, and the progression of joint scores and erosions over five years.

# PATIENTS AND METHODS

Seventy-six patients were included in the study, all of whom were included in the 5 year prospective follow-up study of psoriatic arthritis described in Chapters 2a and b. Peripheral blood was taken during the follow-up visit and subtyping for the 'shared epitope' and other DRB1 alleles performed. The patients were caucasion, had psoriasis, an inflammatory arthropathy and were sero-negative for rheumatoid factor at baseline. A standard clinical and radiological proforma was completed in all patients at baseline and follow-up. Hand radiographs were examined for the presence of erosions.

The control population consisted of 104 healthy caucasian blood donors. All of these were subjected to the screening procedure for blood donors, but mild psoriasis, which has a population prevalence of approximately 2% may have been present.

***Immunogenetics***

DNA was separated from peripheral blood leucocytes using a standard salting out method.

Examination of the HLA-DR locus was performed by two polymerase chain reaction (PCR) based techniques, PCR-SSO (sequence specific oligonucletides) and PCR-SSP (sequence specific primers), which overcome the problems of serological typing, i.e. equivocal results and cross-reactivity (Olerup and Zetterquist 1991, 1992 and 1994 and Zetterquist and Olerup 1992). In PCR-SSO, nucleotide sequence variation in the HLA-DRβ genes is detected using gene amplification of the whole HLA region by the polymerase chain reaction and hybridisation with sequence specific oligonucleotide probes using a dot-blot apparatus. PCR-SSP works on the principle that a perfectly matched primer pair is used in a reaction more sufficietly than a mismatched pair. Two reactions are required both containing an allelic

specific primer whcih leads to the production of a allelic specific product. Genotyping is perfomed by resolving the product on agarose gel.

***Nomenclature***

The alleles encoding the 'shared epitope' contain a consensus sequence of amino acids at positions 70-74 in the third hypervariable region (HVR3) carrying the QKRAA or QRRAA pentapeptide motif. The subtypes encoding this epitope and current and serological nomenclature are shown in Table 1.

***Statisical Analysis***

Genotyping data was entered onto the psoriatic arthritis EXCEL database and the frequency distributions of the various alleles were determined. Chi-squared tests were used to determine differences in the prevalence of the 'shared epitope' and its constitutive alleles between the psoriatic arthritis and control populations. Student's t test was used for comparison of continuous variables for parametric data.

# RESULTS

***Relationship of the Shared Epitope (SE) to Demographic Data***

The characteristics of the patient population is described in detail in Chapters 2a and b and summarised in Table 2.

The ratio of females to males in the psoriatic arthritis patients was 1.53:1. The ascertainment bias that may have contributed to the excess of females in this study has been discussed in Chapter 2a. The 'shared epitope' (SE) was most prevalent in the male population (18/30 (60%) versus 17/46 (37%); $X^2$ test, $p < 0.05$). The age of onset of arthritis was similar in patients with and without the SE and there was no difference in the time difference between the onset of psoriasis and arthritis. Hence the SE was not associated with either an earlier onset of arthritis or a earlier triggering of arthritis in patients with psoriasis. The duration of arthritis was also similar in those with and without the shared epitope, so the clinical comparisons between the two groups are independent of disease duration (Table 2).

***Prevalence of HLADRB1 subtypes and the Shared Epitope***

Thirty-five of the 76 patients (46%) in whom full subtyping data was available had the 'shared epitope' compared with 51 out of 104 controls (49%) (Table 3)

The prevalence of homozygosity and compound heterozygosity were also similar (Table 3).

When combined for analysis, the prevalence of the *04 subtypes (DR4), was significantly less in the patients with psoriatic arthritis compared with controls (Table 2). There was a reduction in the prevalence of *0101 in patients compared with controls, but this did not reach statistical significance (p=0.067) (Table 2).

***Relationship of the Shared Epitope to Clinical Patterns of Disease***

The patients were divided into subgroups as described in Chapters 2a and b. Oligoarthritis was strictly defined as involving four or less joints, and polyarthritis as involving five or more joints; one patient still had monoarthritis after a disease duration of five years. The 'shared epitope' was present in all patterns of disease, with no significant differences between subgroups.

Forty-one of the 76 patients had erosive disease in their hands at baseline which increased to 49 at follow-up. The 'shared epitope' was distributed equally among patients with erosions and those without both at baseline and follow up (19/41 (46.3%) of those with erosions compared with 16/35 (45.7) of those without erosions at baseline and 23/49 (46.9%) of those with erosions and 12/27 (44.4%) of those without erosions at follow-up)(see Table 3). The mean disease durations of psoriatic arthritis was significantly greater for patients with erosions and those without erosions at both baseline (means 17.4 versus 7.22, p=0.001 (t test)) and follow-up (means 19.36 versus 13.6, p=0.027), indicating that the development of erosions is time-dependent. There were no significant differences in the rate of progression of joint scores or erosions in patients with and without the 'shared epitope'.

There was a slight trend for more of the HLA-DR4 positive patients to have erosive disease. Eleven of the sixteen (68.8%) DRB1*04 positive patients had erosive disease compared with 30 of 60 (50%) of the DRB1*04 negative patients, which was not statistically significant.

***Conclusions***

The prevalence of the 'shared epitope' in patients and controls was similar and equal in all subgroups. There was no significant association between the presence of the 'shared epitope' and erosions in the hands, or on the rate of progression of joint

scores or erosions. The *0401 subtype was significantly reduced in psoriatic arthritis patients compared with controls.

## TABLE 1. Nomenclature for HLADRB1 subtypes encoding the 'shared epitope'

| Current Nomenclature | Previous Nomenclature | HLA-D-associated (T cell) Specificity |
|---|---|---|
| DRB1*0101 | DR1 | Dw1 |
| *0102 | DR1 | |
| DRB1*0401 | DR4 | Dw4 |
| *0404 | DR4 | Dw14 |
| *0405 | DR4 | Dw15 |
| *0408 | DR4 | Dw14 |
| DRB1*1001 | DR10 | Not Known |
| DRB1*1402 | DR6, DR14 | Dw16 |

HLA-DRB1*0103 (Dw'BON), DRB1*0104 (Dw20) and the remaining DR4 specificities are excluded

## TABLE 2.
## Distribution of HLADRB1 subtypes encoding the Shared Epitope (SE) and Remaining *01 and *04 Subtypes in Patients and Controls

| SUBTYPE | Number of Patients with Subtype (%) (N= 76) | Number of Controls with Subtype (%) (N= 104) |
|---|---|---|
| DRB1 *0101 | 21 (27.6) | 17 (16.3) |
| *0102 | 1 (1.3) | 4 (3.8) |
| *0103 | 3 (3.9) | 2 (1.9) |
| *0101/0103 | 1(1.3) | 0 |
| TOTAL *01 | 24 (31.6) | 23 (22.1) |
| DRB1 *0401 | 11 (14.5)^ | 29 (27.9)^ |
| *0402 | 0 | 1 (0.96) |
| *0403 | 2 (2.6) | 1 (0.96) |
| *0404 | 3 (3.9) | 8 (7.7) |
| *0405 | 1 (1.3) | 0 |
| *0407 | 0 | 3 (2.9) |
| *0408 | 0 | 0 |
| TOTAL *04 | 16 (17)^ | 38 (36.5)^ |
| DRB1*1001 | 1 (1.3) | 0 |
| DRB1*1402 | 0 | 4 (3.8) |
| SE HOMOZYGOTES/ COMPOUND HETEROZYGOTES | | |
| DRB1*0101/0101 | 1 (1.3) | 0 |
| *0401/0401 | 2 (2.6) | 3 |
| *0401/0404 | 1 (1.3) | 1 (0.96) |
| *0101/0404 | 1 (1.3) | 3 (2.9) |
| *0101/0401 | 1 (1.3) | 2 (1.9) |
| *0401/0102 | 0 | 1 (0.96) |
| *0102/0102 | 0 | 1 (0.96) |
| TOTAL | 6 (7.9) | 11 (10.6) |
| TOTAL SE | 35(46.1) | 48 (46.2) |

*04 and *01 alleles not encoding the "shared epitope" are shown in italics.
^ $p<0.05$

## TABLE 3. Demographic Data and Clinical Features in Relation to the Shared Epitope (SE)

| Feature | SE present | SE absent |
|---|---|---|
| **Sex of Patients** | | |
| Female (N=46) | 17 (37%)* | 29 (63%)* |
| Male (N= 30) | 18 (60%)* | 12 (40%)* |
| Age at Follow-up | 53.5 (21-85) | 54.6 (31-85) |
| Duration of Arthritis at Follow-up (Years; Mean (range)) | 18.2 (5 - 59) | 18.2 (5 - 47) |
| Age of Onset of Arthritis (Years; Mean (range)) | 36.3 (5 - 71) | 35.6 (10 - 71) |
| Onset of Arthritis in Relation to Psoriasis (Years; Mean (range)) | 9.5 (-20 - 52) | 8.8 (-19 - 55) |
| Erosive Disease at Baseline (N=41)(Number/%) | 19 (46.3) | 22 (53.7) |
| Erosive Disease at Follow-up (N=49)(Number/%) | 23 (46.9) | 26 (53.1) |
| Number of Involved Joints (Range) | 17.5 (0-62) | 15.4 (0-57) |
| **Subgroup** | **Number(% subgroup)** | **Number(% subgroup)** |
| Distal Interphalangeal Joint Disease only (N=1) | 1 (100) | 0 |
| Psoriatic Arthritis Mutilans (N=3) | 1 (33) | 2 (66) |
| Oligoarthritis (N=16) | 8 (50) | 8 (50) |
| Polyarthritis (N=49) | 21 (43) | 28 (57) |
| Spondyloarthritis (n=7) | 4 (57) | 3 (43) |
| **TOTAL (N=76)** | 35 (46) | 41 (54) |

*$p < 0.05$

# DISCUSSION

***HLA DRB1 genotypes, the Shared Epitope and disease susceptibility***

In rheumatoid arthritis, the 'shared epitope' (SE) is well recognised as a susceptibility factor for the development of the disease. In the current study, the prevalence of the SE. in psoriatic arthritis was equal to that seen in the control population, so does not appear to confer any susceptibility to the development of psoriatic arthritis overall. However the proportion of DR4 and DR1 alleles was different. Patients with psoriatic arthritis had significantly decreased total HLA DRB1*04 and HLA DRB1*0401 and a trend for an increase in HLA DRB1*01 and HLA DRB1*0101 compared with normal controls; this pattern has been previously reported (Armstrong et al 1983).

***HLA DRB1 Genotypes and the Shared Epitope and Clinical Patterns of Disease***

In RA several authors have looked specifically at radiological progression as a measure of disease severity, some reporting an association of DR4 with erosive change on X-ray (Young et al 1984) and some not (Walton et al 1995). A prospective study in RA failed to find a relationship between the severity or the rate of X-ray progression and DR4 (Stockman 1991). The association is not seen in population-based studies where milder disease is more prevalent (Thomson et al 1993). HLA-DRB1 genotyping in patients attending an early synovitis clinic has been shown to predict erosive disease (Gough et al 1994), but medium term prospective studies have since reported that, although genomic HLA typing is useful to predict the development of persistent RA, there is no clinically useful correlation between the HLA DRB1 type and disease severity (Eberhardt et al 1996). Hence, even in rheumatoid arthritis where the prevalence of the 'shared epitope' is 80% and DR4 is strongly associated in British and North American populations, the relationship to disease severity and progression is not clear cut.

Early studies of HLA DR typing in psoriatic arthritis may have been misleading because of the small numbers of patients reported and the inclusion of rheumatoid factor positive patients who had a pattern of arthritis resembling rheumatoid arthritis, and may have had coincident psoriasis and arthritis. Gerber et al found HLA DR4 in 10 of 12 patients with a pattern of arthritis resembling rheumatoid arthritis, compared with 36% of controls (Gerber et al 1982). In early data from Gladman's group (1986), 7 of 12 patients were HLA DR4 positive compared with 30% of controls, although two of these HLA DR4 +ve patients were IgM rheumatoid factor positive. In a larger Italian population, which has a low population prevalence of HLA DR4, Salvarani (1989) failed to find any association between HLA DR4 and any pattern of psoriatic arthritis. Gladman (1995) has recently failed to find any over -representation of HLA DR4 compared with controls (30% in both) or any association between HLA DR4 and disease progression .

The current study was part of a 5 year prospective follow-up study and the prospective nature allowed for greater certainty of disease classification, stability of diagnosis as well as assessment of disease course and severity. The 'shared epitope' was present in all subgroups of disease, and the proportions of patients in each subgroup did not change with the change in subgroup due to disease progression over five years. In addition there was no relationship between the presence of the shared epitope and the presence of erosions in the hands, which may represent more severe peripheral joint disease, or the rates of progression of joint scores or erosions. However, there was a slight trend for those patients with DR4 to have more erosive disease and a more rapid rate of progression.

***Conclusions***

The HLA DRB1 'shared epitope' does not significantly influence the susceptibility to PsA or the severity of disease in sero-negative patients. The under-representation of DR4 and specifically the HLA DRB1*0401 allele compared with controls

suggests that other HLA DRB1 alleles may have greater importance, such as DR7, although this allele is also over-represented in psoriasis alone (Gladman 1995b). Other non-HLA genotypes may also have relevance to the aetiopathogenesis, but genetic linkage studies involving large populations of psoriatic arthritis patients or multicase families may be required to discover true associations. The lack of association with the SE and psoriatic arthritis is further evidence of its separate identity from rheumatoid arthritis.

## CHAPTER 2e

# THE EFFECT OF HORMONAL FACTORS ON THE ONSET AND COURSE OF PSORIATIC ARTHRITIS.

## SUMMARY

***Introduction*** **.** The relationship of hormone-associated events to disease expression is of particular importance to female patients. The likely effects of hormonal factors have been established in patients with rheumatoid arthritis and it has been suggested that these hormonal events may also be important triggers and modifiers of psoriatic arthritis.

***Hypothesis.*** Hormonal factors may influence the onset of joint and skin disease in psoriatic arthritis.

***Study Aim*** . To determine the relationship between pregnancy and other hormonal factors in

influencing the onset and expression of skin and joint disease in psoriatic arthritis.

***Methods*** **.** The relationship between hormonal factors and the onset and expression of arthritis and psoriasis in 88 women with psoriatic arthritis (including 64 mothers) is assessed. A proforma was completed on all patients, including age of onset of psoriasis and arthritis, pattern of joint disease and relationship of pregnancy, menses and the perimenopausal period to arthritis and psoriasis. Seventy-seven male patients were used as a control population.

***Results*** **.** The age of onset of arthritis in the females was similar to that of the males . There was also no significant difference in the age of onset of the 64 mothers. Psoriasis preceded arthritis by a mean of 10.5 years in the mothers, and 6.2 years in the men. There were 134 pregnancies including seven miscarriages and 2 terminations. Ten mothers developed arthritis prior to the first pregnancy. Of these, 4 had pregnancy-related remissions and post-partum flares and a further 3 had post-partum flares of

peripheral joint disease. One patient with arthritis mutilans developed arthritis during the second trimester of the first pregnancy which deteriorated post-partum. Six patients developed arthritis in association with the post-partum period of the first pregnancy. The mean age of onset of arthritis in these seven patients was 24.4 years, a mean of eight years after the onset of psoriasis. Of the four who had subsequent pregnancies all had a pattern of pregnancy-associated remissions and post-partum flares; this pattern has been confirmed by prospective data in four patients. Eleven patients developed arthritis and 7 had flares of joint symptoms during the perimenopausal period; 13 had pre-menstrual exacerbations.

***Conclusions*.** Pregnancy and other hormonal factors may trigger or modify psoriatic arthritis in a minority of women. In those who develop arthritis prior to or in association with the first pregnancy, a pattern of remissions and post-partum flares of peripheral joint disease is likely in subsequent pregnancies.

# INTRODUCTION

Hormonal factors may also have a role in determining outcome in psoriatic arthritis. There is a growing awareness of the role of pregnancy and other hormone-associated events in mediating the onset, expression and outcome of rheumatic diseases, particularly systemic lupus erythematosus and rheumatoid arthritis which both have a marked female predominance (Petri 1997, Buyan et al 1993, Østensen and Lee Nelson, 1995). Onset of RA closely related to pregnancy has been described and a greater than five-fold increase in risk of RA onset during the first 3 months post-partum has been reported, particularly in the first pregnancy (Silman et al 1992). In rheumatoid arthritis post-partum onset is positively associated with breast feeding, possibly related to hyperprolactinaemia.

There have been fewer studies in the sero-negative spondyloarthropathies, including psoriatic arthritis, but it has been suggested that hormone-associated events may also be important modifiers of the disease (Østensen 1992). A preliminary study of 15 mothers with psoriatic arthritis suggested that pregnancy may trigger an earlier onset of psoriatic arthritis in the post partum period (McHugh and Laurent 1989). Both retrospective and prospective work by Ostensen, found that the pregnancy related remissions and post-partum flares of peripheral joint disease occurred in psoriatic arthritis (Østensen 1992).

The aim of the current study was to assess the relationship between hormonal-associated events including pregnancy and breastfeeding, menstruation and the menopause and the onset and expression of arthritis and psoriasis in psoriatic arthritis.

## PATIENTS AND METHODS

All patients attended the psoriatic arthritis clinic at the Royal National Hospital for Rheumatic Diseases. Eighty-seven women including 64 mothers completed the study. Seventy-seven males were used as a control population. All patients had psoriasis, an inflammatory arthropathy and were sero-negative for rheumatoid arthritis.

The study design was retrospective in 60 mothers and prospective in four mothers. All patients were included on the psoriatic arthritis database containing information regarding the duration of joint and skin disease and the mode of onset and pattern of joint disease. A specific proforma relating to hormonal factors proforma was completed on all female patients at interview. The retrospective data was corroborated where possible by case-note review. Data collected included the number and age of pregnancies, the outcome of the pregnancies, and the age of menarche and the menopause. The pattern and severity of joint and skin disease and relationship to exacerbations or remissions of pregnancy, menstruation and the perimenopausal period was also recorded.

Four patients became pregnant during the study. Objective evaluation of the activity of joint and skin disease was made prior to pregnancy, during pregnancy and post-partum using the following measures. The distribution of joint involvement was noted, activity was assessed modified Ritchie, PASI and nail scores and the biochemical markers viscosity and ESR.

### *Statistical Analysis*

The data was entered onto an Excel database and analysed using Excel and Statworks software packages. For the evaluation of the timing of pregnancy on the time of onset of psoriatic arthritis, three groups were identified for statistical comparison - mothers,

non-mothers and men. The age of onset of arthritis and psoriasis was compared using Student's t test after normality testing.

## RESULTS

The demographic data and subgroup of joint disease data on the females and males in this study is shown in Table 1. All patients had an inflammatory arthritis associated with psoriasis and all but one were sero-negative for rheumatoid factor.

All the women had peripheral joint disease. Thirty had oligoarthritis, fifty-three had polyarthritis and five had arthritis mutilans. No female had distal joint disease exclusively or predominant spondyloarthropathy. The distribution of subgroups in the males was as follows: Distal interphalangeal joint disease only in one; arthritis mutilans in one; polyarthritis in forty; oligoarthritis in twenty-eight; predominant spondyloarthropathy in seven. The age of onset of arthritis in the females (mean 38.4 yrs, range 13-70) was similar to that of the males (mean 36.6 yrs, range 5 - 71 ) and there was also no significant difference in the age of onset of the 63 mothers (mean 39.1, range 13 - 70) (Table 1). Psoriasis preceded arthritis by a mean of 10.5 years in the mothers, 11.8 years in the non-mothers and 6.2 years in the men with no significant differences between the three groups.

The 63 mothers had 133 pregnancies including seven miscarriages and 2 terminations. Four of the miscarriages were in one patient, the cause of which was uncertain (Anti-cardiolipin antibodies were absent). Nine mothers developed arthritis prior to the first pregnancy. Of these, 3 had pregnancy-related remissions and post-partum flares and a further 3 had post-partum flares of peripheral joint disease. There was no apparent association between the disease duration, patient age or timing of arthritis in relation to psoriasis and the tendency for pregnancy to affect the expression of psoriasis in these six women.

One patient with arthritis mutilans developed arthritis during the second trimester of the first pregnancy which deteriorated post-partum. Six patients developed arthritis in

association with the post-partum period of the first pregnancy. The mean age of onset of arthritis in these 7 patients was 24.4 years, a mean of 8.3 years after the onset of psoriasis. Of the four who had subsequent pregnancies all had a pattern of pregnancy-associated remissions and post-partum flares. This pattern has been confirmed by prospective data in four patients, three of whom were first time mothers and the fourth in her third pregnancy (see Table 3).

Eleven patients developed arthritis and 7 had flares of joint symptoms during the perimenopausal period and within two years of the cessation of menstruation. Thirteen patients had pre-menstrual exacerbations.

No relationship between hormone-associated events and the onset or activity of psoriasis was reported in any patient.

***Conclusions***

Pregnancy did not appear accelerate the onset of arthritis in relation to psoriasis. Ten mothers developed arthritis prior to the first pregnancy, 4 of whom had pregnancy-related remissions and post-partum flares and a further 3 had post-partum flares of peripheral joint disease. One patient developed arthritis during the second trimester of the first pregnancy which deteriorated post-partum. Six patients developed arthritis during the post-partum period of the first pregnancy. Of the four who had subsequent pregnancies all had a pattern of pregnancy-associated remissions and post-partum flares.

**TABLE 1. Age of onset of psoriasis and arthritis in mothers, non-mothers and males.** The mean difference in the age of onset of arthritis and psoriasis, and the timing of psoriasis in relation to arthritis for each group is shown

| | Mean age of onset of psoriasis (years) | Mean age of onset of arthritis (years) | Mean difference in age of onset of arthritis and psoriasis (years) | Psoriasis before arthritis (No of patients) | Psoriasis and arthritis simultaneous onset (No of patients) | Psoriasis after arthritis (No of patients) |
|---|---|---|---|---|---|---|
| **FEMALES** | | | | | | |
| **Mothers (N=63)** | **29.1** | **39.1** | **10.5** | **40** | **11** | **12** |
| **Non-Mothers (N=24)** | **24.8** | **36.5** | **11.8** | **18** | **4** | **2** |
| **TOTAL (N=87)** | **27.9** | **38.4** | **11** | **58** | **15** | **14** |
| **MALES** | | | | | | |
| **TOTAL (N=77)** | **30.6** | **36.6** | **6.2** | **47** | **18** | **12** |
| **TOTAL** | **29.1** | **37.6** | **8.5** | **105** | **33** | **26** |

**TABLE 2. Onset and exacerbations of psoriatic arthritis in relation to hormonal events for mothers, all post menopausal women and all women.** Thirty-two mothers were post-menopausal at the time of the study.

| Subgroup of patients | Time of onset or modification of psoriatic arthritis | Number of patients (%) | | |
|---|---|---|---|---|
| | | Onset of arthritis (No./% of group) | Flare of arthritis (No./% of group) | Remission of arthritis (No./% of group) |
| Mothers (N=64) | Before first pregnancy | 10 (15.9) | NA | NA |
| | During 1st pregnancy | 0 | 0 | 4 (6.3) |
| | Post-partum pregnancy one | 6 (9.5) | 7 (11.1) | 0 |
| | During second pregnancy | 1 (1.6) | 0 | 4 (6.3) |
| | Post-partum pregnancy two | 0 | 4 (6.3) | 0 |
| | After all pregnancies | 47(74.6) | NA | NA |
| All post-menopausal women (N=55) | Before menopause | 23 (41.8) | NA | NA |
| | Perimenopausal | 11 (20) | 7 (12.7) | 0 |
| | Post-menopausal | 21 (38.2) | NA | NA |
| All women (N=87) | Before menopause | 55 (63.2) | NA | NA |
| | Pre-menstrual | NA | 13 (15) | 0 |

NA = Not applicable

Post- partum = 0 to 4 months following birth

Perimenopausal = within 2 years of cessation of periods

## TABLE 3. Clinical characteristics and activity of joint and skin disease before, during and after pregnancy in the four patients studied prospectively

| Patient Number | Age before pregnancy | Subgroup arthritis | Medication | Pregnancy number | No of active joints before pregnancy | No of active joints during pregnancy | No of active joints after pregnancy | Plasma Viscosity Before Pregnancy | Plasma Viscosity During Pregnancy | Plasma Viscosity After Pregnancy | DAS Before Pregnancy | DAS During Pregnancy | DAS After Pregnancy | Timing of Flare Post partum |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 31 | AO | Sulphasalazine stopped pre-conception | 3 | 3 | 0 | 3 | 1.63 | 1.54 | 1.73 | 1.76 | 1.04 | 1.73 | 3 months |
| 2 | 34 | AP | Oruvail | 1 | 3 | 4 | 12 | 1.64 | 1.54 | 1.72 | 2.03 | 2.17 | 3.89 | 3 months |
| 3 | 31 | AO | Sulphasalazine stopped pre-conception Piroxicam Codydramol | 1 | 0 | 0 | 0 | 1.63 | ND | 1.75 | ND | ND | ND | Immediate |
| 4 | 35 | SP | Azathioprine continued during pregnancy Methotrexate post-partum | 1 | 0 | 0 | 3 | 1.62 | 1.56 | 1.53 | ND | ND | ND | 3 months |

**Notes**
DAS = disease activity score (Appendix C)

Patient three had widespread pain and tenderness and dactylitis of her toes, but no synovitis

ND = not done

# DISCUSSION

The effect of pregnancy and other hormonal factors on risk and modification of rheumatoid arthritis is complex. Amelioration of the symptoms and signs of rheumatoid arthritis during pregnancy was initially described by Hench in 1938, who found 90% had relief of symptoms. Other retrospective studies have shown amelioration to occur in about three quarters of pregnancies and prospective studies have confirmed this. Most women who improve experience initial relief in the first trimester and rheumatoid arthritis recurs within three to four months of delivery (Lee Nelson and Østensen 1997). This data compares with three out of nine of the patients in the current study who had onset of psoriatic arthritis before the first pregnancy, six or whom had a post-partum flare. In rheumatoid arthritis, seropositivity for rheumatoid factor, patient age, degree of disability and disease duration have not been found to predict the expression of disease during pregnancy . The lack of association with sero-positivity is consistent with our findings in this sero-negative population with psoriatic arthritis. In rheumatoid arthritis, it has been shown that if a women improves during one pregnancy, improvement is likely to occur in subsequent pregnancies as well, which is also suggested in our study.

Amelioration of rheumatoid arthritis occurs early in pregnancy (Hench 1938). Østensen and Husby (1983) compared activity during pregnancy with preconception disease and found initial arthritis relief usually occurred in the first trimester, with further improvement in the second and third trimesters. Once improvement occurred, it persisted, becoming more complete as gestation progressed.

Epidemiological studies have also shown that, although initial onset of rheumatoid arthritis can occur during pregnancy, overall the chance of this occurring is significantly reduced, but increases in the first year post-partum and decreases thereafter. One patient in our study developed onset of psoriatic arthritis during

pregnancy, which deteriorated following the pregnancy. Studies in rheumatoid arthritis have also indicated that there is no indication of any adverse effects of rheumatoid arthritis on pregnancy outcome, which is also suggested by our data in psoriatic arthritis.

***Conclusions***

This data does not support the notion that pregnancy commonly triggers an earlier onset of arthritis in mothers in comparison with non-mothers and men. However, in a minority of susceptible women, it may trigger or modify psoriatic arthritis. In those who develop arthritis prior to or in association with the first pregnancy, a pattern of remissions and post-partum flares of peripheral joint disease is likely in subsequent pregnancies.

# CHAPTER 3

# EXPRESSION OF THE CUTANEOUS LYMPHOCYTE ANTIGEN (CLA) AND ITS COUNTER-RECEPTOR E-SELECTIN IN THE SKIN AND JOINTS OF PATIENTS WITH PSORIATIC ARTHRITIS

## SUMMARY

***Introduction*** The second part of this thesis focuses on immunological mechanisms that may explain the link between joint and skin disease in psoriatic arthritis.

***Hypothesis.*** Selective T cell recruitment to skin and joint tissue and subsequent activation may explain the observed relationship between skin and joint disease in psoriatic arthritis. ***Study Aim.*** To investigate whether skin-homing T lymphocytes identified by the cutaneous lymphocyte antigen (CLA) are increased in the synovial membrane of patients with psoriatic arthritis.

***Methods*** Twenty - six synovial samples (13 psoriatic arthritis, 7 rheumatoid arthritis, 6 osteoarthritis) were obtained from involved knees. Lesional skin biopsies were taken from 9 of the patients with psoriatic arthritis and 6 patients with psoriasis alone. All samples were single and dual-stained for CLA and CD3 (to identify T lymphocytes) using HECA-452 (anti-CLA) and anti-CD3 monoclonal antibodies. E-selectin expression was also determined.

***Results*** The percentage of dual-stained lymphocytes was significantly greater in psoriatic skin than in synovium ($p < 0.001$) and similar between psoriatic and rheumatoid synovium. There was no significant difference in the percentages of CLA-positive cells in psoriatic skin in patients with psoriatic arthritis compared with psoriasis alone. The intensity of endothelial E-selectin expression was significantly greater in skin psoriasis than in synovium ($p < 2 \times 10^{-5}$), and rheumatoid synovium had significantly greater expression than psoriatic synovium ($p < 0.05$). However,

there was no significant correlation between E-selectin expression and the percentages of CLA-positive lymphocytes.

***Conclusion*** This study provides further evidence that the CLA antigen is enriched on skin-homing lymphocytes. Conversely, the link between skin and joint inflammation in psoriatic arthritis does not seem to be explained by increased trafficking of CLA positive T cells to psoriatic synovium.

# INTRODUCTION

The epidemiological and clinical basis for the distinction of psoriatic arthritis other forms of arthritis is well established. The topographic relationship between nail and distal interphalangeal joint disease is well establihsed (Jones et al 1994 and Chapter 2a, Wright 1956, Kay 1997). Espinoza postulated that "noxious substances" may traffic between the sites, linking their involvement (Gerber and Espinoza 1985). Although the inflammatory processes which link skin, nail and joint disease remain elusive, an immune-mediated pathology is implicated.

Immunopathogenic mechanisms involving T lymphocytes in psoriasis and arthritis appear similar. Both the skin and synovium are infiltrated with activated T lymphocytes (Barker 1994, Panayi 1994), with a preponderance of CD4RO+ cells, known to migrate preferentially to peripheral tissues (Panayi 1994). There are known associations with major histocompatibility haplotypes (McHugh 1987, Eastmond 1994). Both psoriasis and arthritis increase in severity with the depletion of T helper lymphocytes secondary to HIV infection (Espinoza et al 1992, Arnett et al 1991), and both improve in response to immunotherapy such as cyclosporin A.

The skin is a functionally unique immune site with apparently a specific homing mechanism for T cells. The cutaneous lymphocyte antigen (CLA), defined by the monoclonal antibody HECA-452 identifies a population of skin-homing memory T cells (Picker et al 1990). The receptor for CLA on dermal endothelium is the inducible cell adhesion molecule E-selectin (Picker et al 1991), a protein which also acts to tether neutrophils during their initial rolling interaction with the blood vessel wall at the onset of an inflammatory response (Berg et al 1991, Bevilacqua et al 1994). It has been proposed that E-selectin on venules at sites of acute inflammation supports neutrophil recruitment , whereas in sites of chronic inflammation in the skin mediates accumulation of CLA-positive T cells (Picker et al 1991).

The principal aim of the current study was to determine whether skin and joint disease in psoriatic arthritis may be linked through the inappropriate expression of CLA molecules, E selectin or both. We have therefore investigated the percentages and distribution of skin-homing (CLA-positive) T lymphocytes and their counter-receptor E-selectin in the skin, synovium and peripheral blood of patients with psoriatic arthritis and appropriate controls.

# METHODS

## ETHICAL APPROVAL

The study was approved by the Bath and South West Ethical Committee. Written consent was obtained for biopsies.

## PATIENTS

Thirteen patients with psoriatic arthritis and synovitis of a knee were recruited from a psoriatic arthritis clinic. Clinical information including the age, sex, duration of psoriasis and arthritis, subgroup of joint disease, presence of erosions, degree of knee synovitis, skin severity, periodicity of skin and joint disease and the presence of nail disease was recorded. All patients had active psoriasis, and were sero-negative for rheumatoid factor.

Controls included samples from 7 patients with sero-positive rheumatoid arthritis defined by the American College of Rheumatology (Arnett et al 1988), six patients with osteoarthritis and six patients with psoriasis alone. No patient or control had received an intra-articular steroid injection within three months of obtaining synovial samples.

## IMMUNOHISTOCHEMISTRY

### Sample Collection

1. ***Synovium***

Biopsies were taken from knee joints by a standard blind needle biopsy technique using a Polley's needle after local anaesthesia. At least six samples of synovial membrane were obtained from different regions of the suprapatellar pouch. Paraffin

sections were obtained for descriptive histology. Samples from two of the patients with RA and three of the six patients with osteoarthritis were obtained at the time of arthroscopy or joint replacement.

**2. *Skin***

Elliptical skin samples were obtained from 9 patients with psoriatic arthritis, 8 of whom had concurrent synovial biopsies, and 6 patients with psoriasis alone, recruited from a dermatology clinic. A musculoskeletal history and joint examination was performed to confirm the absence of arthritis in the latter patients. Biopsies were taken from lesional edges of the most active accessible plaques. In one patient the skin biopsy was taken from a plaque directly on the involved knee.

Further control tissue included three samples of normal skin from healthy volunteers, one sample of lesional skin from a patient with severe eczema, and a sample of normal tonsil.

**Preparation of sections**

Tissue sections of skin and synovium were mounted on cork with 5% polyvinyl alcohol (PVA), snap frozen in liquid nitrogen and stored at -70$^{o}$C. The cork was mounted on to a metal chuck with PVA, and 8μm sections were cut on a cryostat at -25$^{o}$C. Sections were mounted serially on 4-well glass slides, air-dried for one hour and fixed in acetone at room temperature for 10 minutes, wrapped in tin-foil and stored at -20$^{o}$C prior to use. Histology was checked every 10 sections using a rapid staining technique (Diffquick). Synovial specimens without clearly defined synovial lining cells and skin specimens without identifiable epidermis and dermis were discarded.

**Materials and Methods**

The antibodies and other reagents used are listed in Table 1. The monoclonal antibody HECA-452 was provided by Dr Louis Picker, University of Texas, USA.

**Single-staining for CD3 and CLA**

CD3 populations were quantified using anti-CD3 supernatant (undiluted) or control mouse IgG (dilution 1 in 500) and alkaline phosphatase/ monoclonal anti-alkaline phosphatase (APAAP) complexes using a standard method described by the manufacturer (Dakopatts.)

Sections were stained for CLA using HECA-452 (rat IgM) and a standard biotin/streptavidin-alkaline phosphatase technique:- (1)blocking step for 20 minutes with human AB serum in 5% solution with Tris-buffered saline (TBS); (2) one hour incubation with HECA-452 monoclonal antibody (rat IgM) at 1/30 dilution or control rat IgM (1/100 dilution); (3) 30 minute incubation with biotinylated species-specific anti-rat immunoglobulins at 1/50 dilution ; (4) 30 minute incubation with streptavidin-alkaline phosphatase at 1/50 dilution ; (5) Fast red/substrate for 15 to 20 minutes at room temperature. All reagents were diluted in TBS and 100μl of diluent used for each section. Each stage was followed by washing for 1-2 minutes in TBS. Finally the sections were lightly counterstained with haematoxylin and mounted.

Double fluorescence staining was used to estimate the percentage of CLA-positive T lymphocytes because the HECA-452 monoclonal antibody is not T-cell specific, also identifying related E-selectin ligands on high endothelial venules (HEVs), neutrophils and monocytes.

**Fluorescence Double-Staining**

Sections were double-stained for CLA and CD3 using HECA-452 and anti-CD3 supernatant and fluorescein isothiocyanate (FITC) and tetramethylrhodamine

isothiocyanate (TRITC) conjugates respectively and appropriate non-reactive control monoclonal antibodies. Each serial 4 well slide had a control section, single-stained sections for CLA and CD3 and a double-stained section. The incubation steps for double-staining were:- (1) 20 minute blocking step with human AB serum in 5% solution with PBS (2) 45 minute incubations with anti-CD3 supernatant (undiluted) and goat TRITC anti-mouse IgG (1 in 50) ; (3) 20 minute blocking step with 5% normal mouse serum (NMS) (4) HECA-452 monoclonal antibody (1/30 dilution) (5) 45 minute incubation with rabbit biotinylated species-specific anti-rat immunoglobulins (1/50); (6) FITC-streptavidin (1/50) . All antibodies were diluted in phosphate-buffered saline (PBS) and each stage was followed by washing for 1-2 minutes with PBS. The sections were mounted using 1,4-diazabicyclo (2, 2, 2) octane (DABCO) as an interface.

Three psoriatic synovial sections were similarly double-stained for macrophages using anti-CD68 instead of anti-CD3.

Sections were stained in duplicate or triplicate, blinded to the diagnosis and scored by two investigators (the author and Jonathon Dixey). The number of single and double-stained T lymphocytes were assessed in the dermis of the skin and sublining layer of the synovium. Sequential fields were studied using an eyepiece orientated along the dermo-epidermal junction or synovial lining layer. A section was only scored if the singly stained section was of equivalent intensity to the dual stained section. Inter observer variability was within 10%.

### Determination and Quantification of E-Selectin Expression

The anti-E-selectin monoclonal antibody was used, followed by the APAAP complex according to the protocol described by the manufacturers (Dakopatts), followed by haematoxylin counterstaining. Endothelial morphology was confirmed in longitudinally cut vessels by the endothelial cell marker anti-CD34. Anti-E selectin was used at a dilution of 1/200, anti-CD34 and APAAP at 1/50. Vessels in the dermis of the skin and synovial sublining were scored in sequential fields. The number of vessels, the proportion of E-selectin positive vessels and the intensity of staining was determined on an arbitrary scale as follows:- 0 = no staining detected; 1 = minimal staining; 2 = moderate staining; 3 = strong staining. The mean intensity was computed for each section. The density of the surrounding inflammatory infiltrate was also determined using the following scale:- 0 = no inflammatory infiltrate; 1 = small inflammatory infiltrate; 2 = moderate inflammatory infiltrate; 3 = dense inflammatory infiltrate.

## FLOW CYTOMETRY

### Sample Collection

Ten mls of venous blood was taken from 12 patients with psoriatic arthritis, 6 with rheumatoid arthritis and 6 normal controls. All the psoriatic arthritis and rheumatoid arthritis patients had clinical evidence of active synovitis. Three of the psoriatic arthritis patients were included in the immunohistological study (Table 2, patients 3, 4 and 7).

### Materials

The reagents used are listed in Table 1. The FITC-conjugated HECA-452 monoclonal antibody and a control FITC-conjugated rat IgM with unspecified reactivity were donated by Dr Picker and used undiluted.

**Methods**

Mononuclear cells (MNC) were separated from 10mls heparinised whole blood using a standard lymphoprep gradient. Ten mls of heparinised blood was taken from each patient. The separated MNCs were washed with medium, counted and re-suspended in RPMI and 10% foetal calf serum and preincubated with 50µl undiluted normal human serum. Five x $10^5$ cells were used per test. The following reagents were added:- (1) anti-CD3, (2) phycoerythrin (PE)-conjugated anti-mouse immunoglobulins (1/50) and (3) FITC-conjugated HECA-452 monoclonal antibody (undiluted) with appropriate controls minus one or more reagents. After 30 minutes incubation, the cells were resuspended in PBS containing 1% paraformaldehyde.

Flow cytometry was performed using a Becton-Dickinson FACStar Plus with air-cooled argon laser and Consort 32 computer. Gating was performed by setting the threshold with reference to the relevant negative control. The percentages of CLA positive circulating T lymphocytes in peripheral blood of patients with psoriatic arthritis, rheumatoid arthritis and normal controls were determined.

**DATA ANALYSIS**

Data were analysed using a Hewlett Packard personal computer with software packages including Microsoft Excel and Statmost. Normality testing was performed prior to analysis. Duncan's test for multiple comparisons was used for the various patient groups. The Mann Whitney U test was used to compare all the psoriatic skin versus the synovial samples. The Wilcoxon signed rank test was used for paired psoriatic skin and synovial data. Spearman's rank coefficient was used for correlation analysis.

# RESULTS

## Clinical Characteristics

The patients represented a spectrum of disease severity for both joint and skin disease (Table 2). There were 6 females and 7 males, mean age 44 (range 20 to 62 years). The mean duration of arthritis 15 years (range 6 - 27) and psoriasis 18 years (range 0 - 36). One patient (patient 13) had trivial psoriasis only that at the time of synovial biopsy and did not reach the criteria for a PASI score. The immunohistological data were assessed in relation to clinical parameters.

## Immunohistology

### *T lymphocyte populations*

The distribution of T lymphocytes in each sample was quantified prior to double-staining (Table 3). Eight synovial samples (6 osteoarthritis, 2 psoriatic arthritis) did not have sufficient lymphocytic infiltration to accurately determine the percentages of CLA positive T cells. The two psoriatic arthritis patients had mild synovitis only at the time of biopsy. For the 6 osteoarthritis patients, only isolated lymphocytes were present, with an occasional double-stained cell. Apart from the osteoarthritis group, the mean numbers of T cells per field (T cell density) were similar in the other four patient groups. There was a weak negative correlation between the T cell density in synovium and the duration of arthritis but this was not significant. There was also a weak positive correlation between the degree of synovitis clinically in psoriatic arthritis and the T cell density, but this was not statistically significant.

### *Immunohistological distribution of the CLA antigen*

The CLA antigen was present on many cell types within the synovium, including T cells, vascular endothelium, neutrophils and macrophages. Its presence on macrophages was also confirmed by double-labelling with an anti-CD68 monoclonal antibody. In the skin, CLA-positive lymphocytes were observed in all lymphocytic

areas; this included perivascular lymphoid aggregates around superficial dermal vessels, immediately below the stratum basale, and in the more diffuse cellular infiltrate. Other skin cell types also stained for HECA-452 including macrophages, polymorphonuclear leucocytes, vascular endothelial cells and Langerhans cells.

***CLA/CD3 double -staining***

The percentages of CLA/CD3 double-stained lymphocytes in patient groups and control tissue are shown in Table 3 and Figure 1. Representative results of fluorescence double- staining of CD3 and CLA for psoriatic skin and synovium are shown in Figures 2a-d. There was a significant correlation between the density of the inflammatory infiltrate and the percentages of CLA positive T cells ($p<0.05$).

The following comparisons between disease groups were made: (a) all skin (N=19) and all synovial samples (N=18); (b) psoriasis (N=15) and psoriatic arthritis synovium (N=11); (c) psoriatic arthritis synovium (N=9) and rheumatoid arthritis synovium (N=7); (d) paired psoriatic arthritis synovial membrane and skin samples (N=7) and (e) psoriasis in patients with arthritis (N=8) and those without arthritis (N=6).

The percentages of lymphocytes double-stained for CLA and CD3 were significantly greater in (a) skin than in synovium ( $p<10^{-6}$ ) and (b) psoriasis than in psoriatic arthritis synovium ($p=0.01$). For paired skin and synovial samples from psoriatic arthritis patients, the percentages of double-stained lymphocytes were also significantly greater in skin than in synovium ($p< 0.02$). In one paired sample of psoriatic skin and synovium (Patient 8) the percentage expression was 48.5% and 34% respectively.

There were no significant differences between the percentages of double-stained lymphocytes in psoriatic arthritis synovium compared with rheumatoid arthritis

synovium. In skin psoriasis there were no significant differences in the percentages of CLA positive lymphocytes in patients who had arthritis compared with those with psoriasis alone. The percentages in the three samples of normal skin and from one sample of eczematous skin were similar (all 60%), but much less in tonsil (2.5 %).

There were no significant associations between any clinical parameter and the percentages of double-stained lymphocytes in synovial tissue. There were no significant associations between the degree of synovitis clinically and the percentage of double-stained lymphocytes. In particular, there were no significant differences between the percentages of double-stained lymphocytes in the four patients who had coincident exacerbations of their skin and joint disease and those in whom there was no apparent temporal association. The patient with the greatest percentage of double-stained lymphocytes in synovium (34%) did have simultaneous exacerbations of his skin and joint disease.

***E selectin expression***

The mean number of blood vessels per field, the percentage of positively stained vessels, the E-selectin intensity and the density of the perivascular infiltrate are shown in Table 4. Comparisons between the percentages of positive vessels, E-selectin intensities, numbers of vessels and perivascular infiltrates were made in the following groups - (a) all skin (N=18) and all synovial samples (N=16); (b) all psoriasis (N=15) and psoriatic arthritis synovium (N=10); (c) psoriatic arthritis synovium (N=10) and rheumatoid arthritis synovium (N=6); (d) paired psoriatic arthritis synovial membrane and skin samples (N=6) and (e) psoriasis in patients with arthritis (N=8) and those without arthritis (N=6).

The results for the disease group comparisons for the intensity of E-selectin expression were as follows: (a) E-selectin expression was significantly greater in

skin than synovium ($p < 2 \times 10^{-6}$) and (b) in skin psoriasis compared with psoriatic synovium ($p < 2 \times 10^{-5}$); (c) E-selectin expression was significantly greater in rheumatoid arthritis synovium compared with psoriatic arthritis synovium ($p < 0.05$); (d) E-selectin expression was significantly greater in skin than synovium ($p < 0.018$) in paired skin and synovial samples from patients with psoriatic arthritis; (e) there was no significant difference in E-selectin expression in the skin of patients with arthritis compared with those without arthritis. The results of these comparisons were similar when the numbers of positive vessels was used instead of E selectin intensity. No E-selectin expression was seen in 3 of 10 psoriatic arthritis synovial samples and 1 of 7 rheumatoid arthritis synovial samples. Minute quantities only of E-selectin were detected in osteoarthritis synovial membrane. In skin E-selectin was expressed in all samples throughout the dermal vessels, including the deep dermal vasculature, and was present in all samples. E-selectin expression in skin and synovium is shown in Figure 3.

The numbers of vessels per field were significantly greater in synovium than all the skin samples, including the three samples of exzema and normal skin ( $p < 0.03$). Furthermore the difference remained significant when only psoriatic skin was analysed ( $p < 0.04$). However, there were no significant differences between the numbers of vessels per field between any of the remaining disease groups.

There were no significant differences in the density of the perivascular infiltrates between the patient groups. For psoriatic arthritis synovium there was a significant correlation between E-selectin expression and the density of the inflammatory infiltrate ($p < 0.005$). For all the disease groups combined, there was a weak positive correlation between E-selectin expression and the density of the inflammatory infiltrate, but this was not significant. There were no significant correlations between E-selectin intensity and any clinical parameter or the percentages of CLA positive T cells.

*CLA positive T cells in Peripheral Blood*

Flow cytometry results for T lymphocytes double-stained for CD3 and CLA are shown in Figure 4. Patients with rheumatoid arthritis had slightly greater percentages of double-stained cells (median 4.8, range 2.6 - 8.4 %) than those with psoriatic arthritis (median 2.9, range 1.4 - 5.8%) and four normal control patients (median 2.0, range 1.1 - 5.7% ). The differences between the disease and normal control groups were not significant.

*Conclusions*

The major findings are summarised as follows. The percentage of dual-stained lymphocytes was significantly greater in psoriatic skin than in synovium and similar between psoriatic and rheumatoid synovium. There was no significant difference in the percentages of CLA-positive cells in psoriatic skin in patients with psoriatic arthritis compared with psoriasis alone. The intensity of endothelial E-selectin expression was significantly greater in skin psoriasis than in synovium, and rheumatoid synovium had significantly greater expression than psoriatic synovium. However, there was no significant correlation between E-selectin expression and the percentages of CLA-positive lymphocytes.

**TABLE 2. Clinical characteristics of psoriatic arthritis patients.**

| Patient | Age | Sex | Duration Arthritis/ years | Duration Psoriasis/ years | Subgroup | Erosions | Knee Synovitis | Historical Skin Severity | PASI Score (0-72) | Nail Disease | Nail Score (0-40) | Simultaneous Skin and Joint Exacerbations |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 59 | F | 27 | 28 | Mutilans | y | 2 | 3 | 4.2 | n | 0 | n |
| 2 | 62 | F | 18 | 10 | Polyarthritis | y | 3 | 3 | 4.8 | n | 0 | n |
| 3 | 53 | M | 24 | 36 | Polyarthritis | y | 1 | 2 | 4.2 | y | 4 | y |
| 4 | 40 | M | 6 | 16 | Polyarthritis | y | 2 | 2 | 4.4 | y | 17 | n |
| 5 | 38 | M | 7 | 8 | Oligoarthritis | n | 1 | 2 | 2.1 | y | 6 | n |
| 6 | 20 | F | 6 | 8 | Oligoarthritis | n | 3 | 1 | 2.7 | y | 7 | y |
| 7 | 30 | M | 26 | 9 | Polyarthritis | n | 1 | 3 | 4.1 | y | 0 | y |
| 8 | 62 | M | 22 | 22 | Polyarthritis | y | 3 | 3 | 1.2 | y | 5 | n |
| 9 | 42 | F | 7 | 20 | Oligoarthritis | n | 1 | 1 | 0.6 | y | 0 | n |
| 10 | 40 | M | 12 | 12 | Oligoarthritis | n | 2 | 2 | 2.1 | n | 0 | n |
| 11 | 48 | M | 20 | 33 | Polyarthritis | y | 2 | 2 | 2.4 | y | 18 | n |
| 12 | 46 | F | 15 | 30 | Polyarthritis | y | 2 | 2 | 0.5 | y | 7 | y |
| 13 | 34 | F | 6 | <1 | Polyarthritis | y | 3 | Trivial | 0 | y | 3 | n |

Patients 3 and 7 had insufficient synovial lymphocytes for quantitative assessment.
Paired skin samples were available on patients 1-8
Historical skin severity and knee synovitis are graded on a three point scale - 1 = mild, 2 = moderate and 3 = severe

**TABLE 3: T Lymphocyte densities and percentages of CLA positive cells in psoriatic arthritis, rheumatoid arthritis synovium and psoriatic skin**

| | Sample Number | Number of T cells per h p f (X40) Mean(range) | Number of T Cells Counted | % CLA Positive T Cells |
|---|---|---|---|---|
| ***Psoriatic Synovium** | | | | |
| | 1 | 18(11-32) | 107 | 11.2 |
| | 2 | 20(13-26) | 101 | 4 |
| | 3 | <1 | ND | ND |
| | 4 | 92 (32-231) | 369 | 3.8 |
| | 5 | 10 (8 - 11) | 39 | 15 |
| | 6 | 38 (16-55) | 269 | 3.3 |
| | 7 | 8 (1-39) | 631 | 7.1 |
| | 8 | 4 (1-13) | 159 | 34 |
| | 9 | <1 | ND | ND |
| | 10 | 25 (12-40) | 253 | 7.5 |
| | 11 | 11(1-53) | 310 | 4.2 |
| | 12 | 11(3-21) | 157 | 5.7 |
| | 13 | 9 (5-13) | 53 | 11 |
| Mean (SD) | | 22 (25) | 307 (173) | 9.7 (8.9) |
| **RA Synovium** | | | | |
| | 1(surgical) | 1 (0-45) | 362 | 14 |
| | 2 | 44 (33-52) | 261 | 2.7 |
| | 3 | 16(9-25) | 197 | 10 |
| | 4 | 7(3-11) | 51 | 3.9 |
| | 5 | 41(19-67) | 285 | 4.9 |
| | 6 (surgical) | 27(11-65) | 348 | 14.4 |
| | 7 | 30 (21-38) | 180 | 2.2 |
| Mean (SD) | | 24 (16.4) | 241 (108) | 7.4 (5.3) |
| ***Psoriasis in Psoriatic Arthritis** | | | | |
| | 1 | 10(5-14) | 52 | 51.9 |
| | 2 | 11 (6-16) | 56 | 46.4 |
| | 3 | 17 (7-34) | 121 | 41.3 |
| | 4 | 21 (13-26) | 170 | 50.6 |
| | 5 | 23 (3 - 58) | 132 | 56.1 |
| | 6 | 35 (19-66) | 283 | 57.6 |
| | 7 | 12 (6-24) | 167 | 32.3 |
| | 8 | 25 (11-40) | 197 | 48.2 |
| | 9 | 35 (13-47) | 212 | 42.9 |
| Mean (SD) | | 19 (9.6) | 147 (74) | 47.5 (7.9) |
| **Psoriasis** | | | | |
| | 1 | 26 (6-15) | 104 | 43.3 |
| | 2 | 36 (24-39) | 254 | 57.8 |
| | 3 | 11(8-20) | 100 | 38 |
| | 4 | 20(9-28) | 256 | 39.5 |
| | 5 | 6 (2-11) | 51 | 60.8 |
| | 6 | 24 (17-39) | 166 | 75.3 |
| Mean (SD) | | 21 (10.1) | 155 (85.5) | 52.4 (14.7) |

*Psoriatic synovial samples 1 - 8 are paired with psoriatic arthritis skin samples 1 - 8.
ND = not done

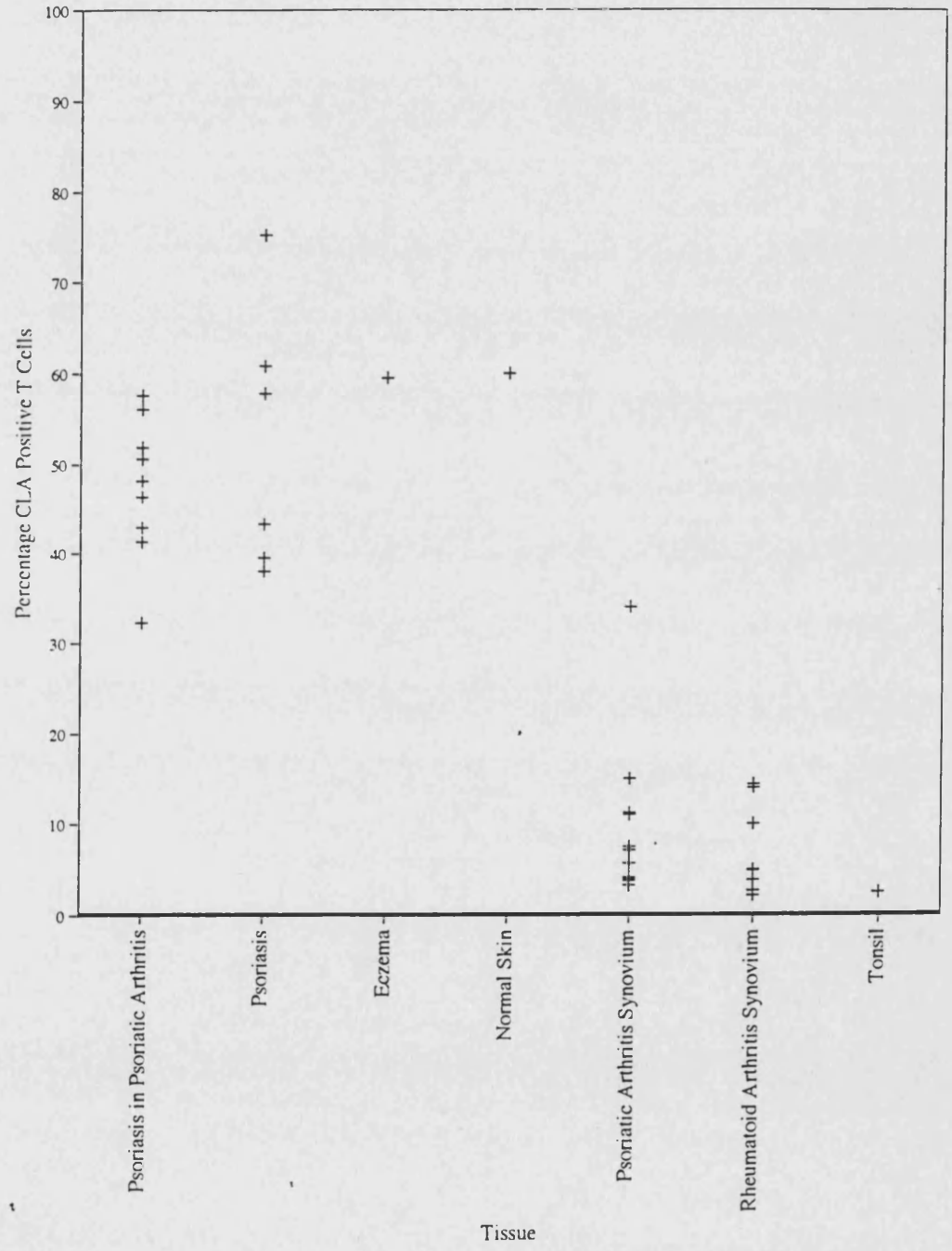
**TABLE 4. Number of vessels per field, expression of E selectin and density of perivascular infiltrate in psoriatic arthritis, rheumatoid arthritis synovium and all skin samples.**

| | Number | Number of Vessels per HPF (X20) (Mean) | Number of Vessels Counted | Percentage of Positive Vessels | E selectin Intensity (Mean) | Density of Perivascular Infiltrate (Mean) |
|---|---|---|---|---|---|---|
| *Psoriatic Synovium | | | | | | |
| | 1 | 10 | 30 | 33 | 1 | 1.93 |
| | 2 | 4.3 | 18 | 50 | 0.65 | 1.35 |
| | 3 | ND | ND | ND | ND | ND |
| | 4 | 4.3 | 13 | 0 | 0 | 0.85 |
| | 5 | ND | ND | ND | ND | ND |
| | 6 | 4.2 | 25 | 16 | 0.2 | 0.76 |
| | 7 | 7.1 | 50 | 0 | 0 | 1.2 |
| | 8 | 8.75 | 70 | 13 | 0.65 | 1.35 |
| | 9 | ND | ND | ND | ND | ND |
| | 10 | 6.5 | 65 | 35 | 0.54 | 1.37 |
| | 11 | 4.5 | 18 | 22 | 0.22 | 1.22 |
| | 12 | 10 | 10 | 0 | 0 | 0.2 |
| | 13 | 10 | 10 | 20 | 0.2 | 1.3 |
| Mean (SD) | | 7 (2.6) | 30.9(22.7) | 18.9(16.8) | 0.35 (0.34) | 1.16 (0.46) |
| Rheumatoid Arthritis Synovium | | | | | | |
| | 1(surgical) | ND | ND | ND | ND | ND |
| | 2 | 5 | 10 | 50 | 0.7 | 0.7 |
| | 3 | 5.5 | 11 | 9 | 0.09 | 0.36 |
| | 4 | ND | ND | ND | ND | ND |
| | 5 | 15.3 | 92 | 64 | 1.38 | 1.63 |
| | 6 (surgical) | 5.9 | 142 | 48 | 0.77 | 0.77 |
| | 7 | 2.3 | 7 | 0 | 0 | 2.86 |
| | 8 | 6.9 | 104 | 62 | 1.31 | 1.14 |
| Mean (SD) | | 6.8 (4.4) | 61(59) | 38.8(27.5) | 0.71 (0.58) | 1.24 (0.9) |
| *Psoriasis in Psoriatic Arthritis | | | | | | |
| | 1 | 3 | 9 | 100 | 2.44 | 1.56 |
| | 2 | 5 | 45 | 100 | 2.06 | 0.66 |
| | 3 | 8.3 | 33 | 100 | 1.82 | 1.39 |
| | 4 | 3.9 | 27 | 100 | 2.44 | 1.19 |
| | 5 | 6 | 30 | 100 | 2.67 | 1.8 |
| | 6 | 6.6 | 39 | 87 | 1.66 | 1.27 |
| | 7 | 4.8 | 43 | 100 | 1.95 | 1.02 |
| | 8 | 11.3 | 102 | 84 | 1.95 | 1.22 |
| | 9 | 5 | 15 | 100 | 2.87 | 2.13 |
| Mean (SD) | | 6 (2.5) | 40.3 (27.7) | 96.8(6.4) | 2.21 (0.41) | 1.36 (0.43) |
| Psoriasis | | | | | | |
| | 1 | 2.5 | 10 | 100 | 1.6 | 1.7 |
| | 2 | 2.8 | 14 | 100 | 1.29 | 1.86 |
| | 3 | 1.5 | 12 | 100 | 2.5 | 1.25 |
| | 4 | 4 | 16 | 94 | 1.81 | 1.44 |
| | 5 | 4.2 | 21 | 100 | 2.48 | 1.29 |
| | 6 | 3.7 | 46 | 100 | 1.6 | 1.33 |
| Mean (SD) | | 3.7 (1.0) | 28.8 (13.3) | 99(2.4) | 2.09 (0.5) | 1.53 (0.25) |
| Eczema | 1 | 5.4 | 27 | 89 | 2.3 | 1.78 |
| Normal | 1 | 3.7 | 11 | 18 | 0.18 | 0.73 |
| | 2 | 2 | 10 | 80 | 0.9 | 0.6 |
| Mean (SD) | | 2.9 (1.2) | 10.5 (0.71) | 49(43.8) | 0.54(0.51) | 0.67 (0.09) |

*Psoriatic synovial samples 1 - 8 are paired with psoriatic arthritis skin samples 1 - 8.
All samples correspond to those in Table 3.

**FIGURE 1**

Percentages of T lymphocytes that are CLA positive in psoriasis with and without arthritis, eczema, normal skin, psoriatic arthritis synovium, rheumatoid arthritis synovium and tonsil.

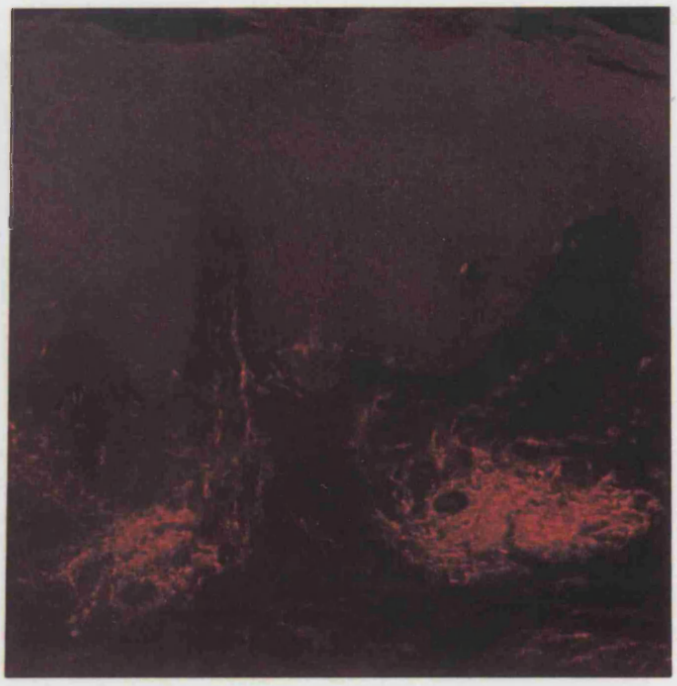


**FIGURES 2a-d**

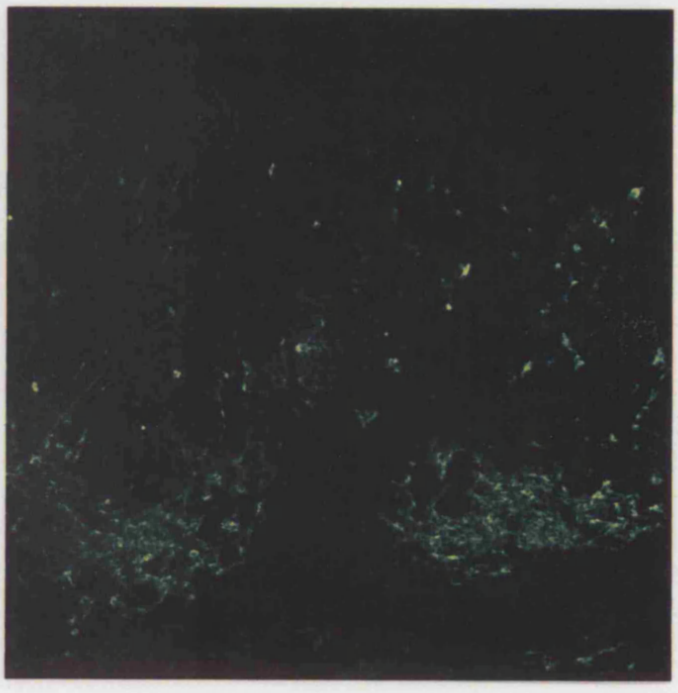
Photomicrographs of fluorescence dual staining of psoriatic skin and psoriatic arthritis synovium. (a) TRITC anti-CD3 labelled lymphocytes in skin psoriasis (stained red; green filter) (original magnification X 20); (b) FITC HECA-452 labelled cells in psoriasis (original magnification X 20). The majority of T lymphocytes in the aggregate are CLA positive. (c) TRITC anti-CD3 labelled lymphocytes in psoriatic arthritis synovium (stained red; green filter) (original magnification X 40) ; (d) FITC HECA-452 labelled cells in psoriatic arthritis synovium (stained green; red filter) (original magnification X 40). Almost all the lymphocytes are CLA negative. A rare pair of dual-stained lymphocytes are shown (long arrows). A non-lymphocytic cell labelled with the HECA-452 monoclonal antibody is also shown (short arrow).
The bar represents 100μm.

**FIGURE 3a - c**

Differing intensities of E-selectin expression on vascular endothelium in (a) psoriasis, (b) rheumatoid arthritis synovium and (c) psoriatic arthritis synovium. A typical vessel in each section is indicated by the arrows.
The bar represents 100μm.

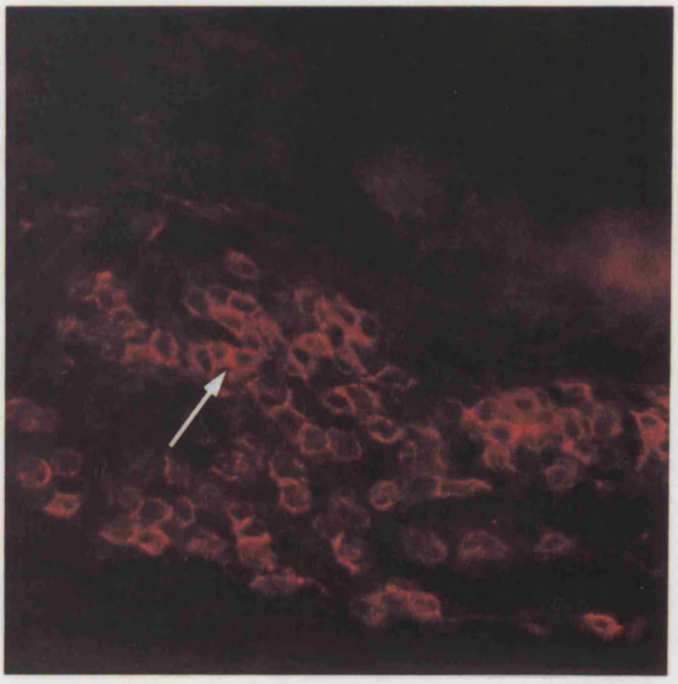


(a)



(b)

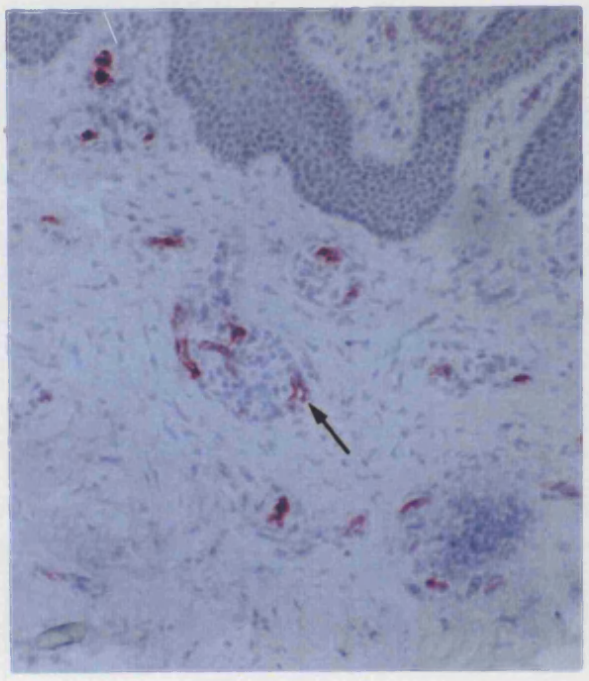
**FIGURE 2**



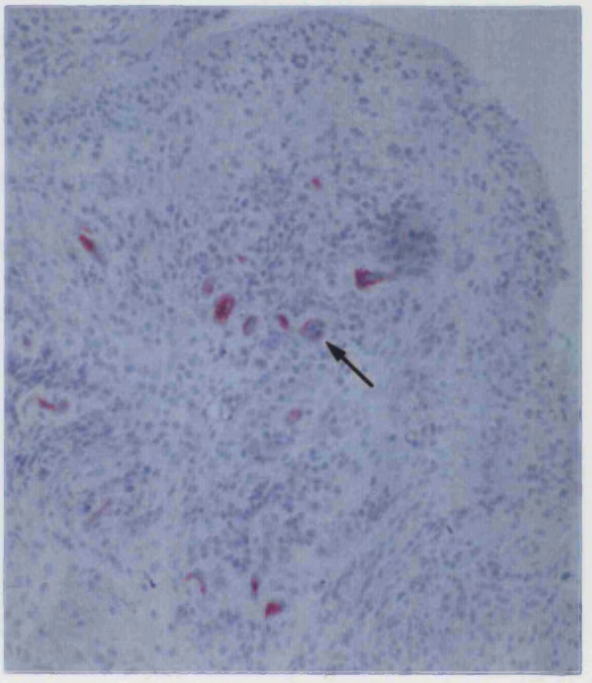
(c)

(d)

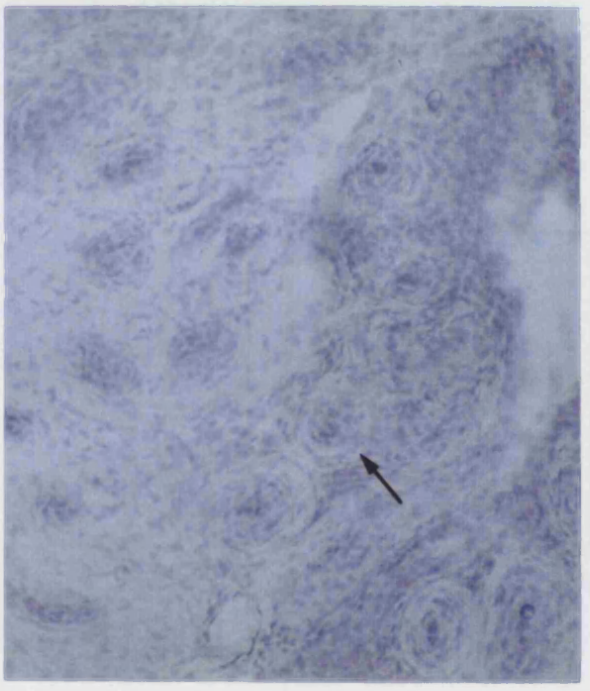
**FIGURE 2**



(a)



(b)

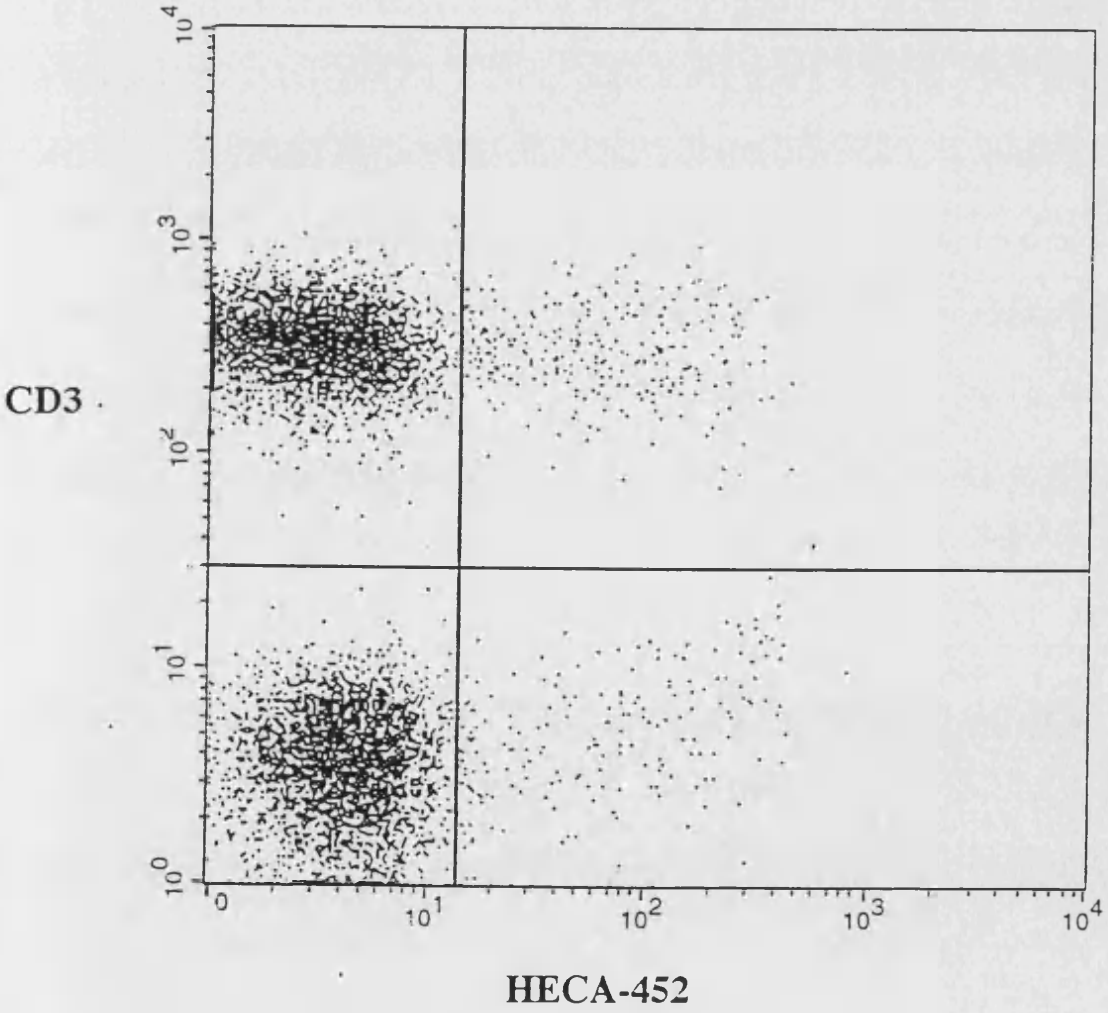


(c)

**FIGURE 3**

**FIGURE 4**

A representative two-dimensional flow cytometric profile of lymphocytes from the peripheral blood of a patient with rheumatoid arthritis. The upper left quadrant shows CD3 positive /HECA-452 negative lymphocytes; the upper right quadrant shows dual-stained CD3 positive/ HECA-452 positive lymphocytes and the lower right quadrant shows single-stained CD3 negative/HECA-452 positive lymphocytes. In this sample 4.8% of CD3 positive lymphocytes are dual-stained for HECA-452.



# DISCUSSION

Patients with psoriatic arthritis provide a unique opportunity for studying tissue specific homing mechanisms that contribute to chronic inflammation. I have obtained paired samples of chronically inflamed skin and synovium from such patients, which span all the patterns and severities of peripheral joint disease with the common features of knee synovitis and active skin disease. Our major finding is that there is a significantly greater percentage of CLA positive lymphocytes in psoriatic skin compared with synovium in psoriatic arthritis, and that this difference is independent of the clinical characteristics. The data confirms previous evidence that the CLA molecule is enriched only on skin-homing T lymphocytes (Picker et al,1990) and is similar to the results reported in another recent study of psoriatic arthritis (Pitzalis et al 1996). Differential expression of the CLA antigen represents the single most prominent difference between the T lymphocyte infiltrate in psoriatic skin and synovium. Furthermore there was no significant difference in the numbers of CLA positive T lymphocytes in peripheral blood between psoriatic arthritis, rheumatoid arthritis and normal healthy control patients. I conclude that there does not appear to be any circulating clonal expansion of CLA positive lymphocytes in patients with psoriatic arthritis.

The lack of association between the expression of the CLA molecule in psoriatic skin and synovium may be consistent with existing observations regarding the link between psoriasis and arthritis. For instance there is no association between the type or distribution of skin involvement and arthritis subgroup (Jones et al 1994 and Chapter 2a). Also a pattern of joint disease typical of mutilating psoriatic arthritis may occur without skin disease or with nail disease only (O'Neill et al 1992). In the majority of patients the skin disease presents first and although up to 35% of patients report exacerbations of both skin and peripheral joint disease joint disease, this temporal relationship only occurs slightly more often than would be expected by

chance (Gladman et al 1987, Chapters 2b and c). The prospective study of Chapter 2c shows that a temporal relaitionship is only found consistently in a small minority of patients. In the current study, I have included two patients who reported simultaneous exacerbations of skin and joint disease, one of whom had a higher percentage of CLA positive lymphocytes than any other synovial sample; however the intensity of expression was noted to be less than in skin psoriasis. In previous work one sample of liver was found to have 40% CLA positive T lymphocytes (Picker et al 1990). Our patient had a severe active synovitis in his knee suggesting that during acute inflammation general mechanisms might overide specific homing mechanisms.

E-selectin is up-regulated on the vascular endothelium of inflammatory skin lesions (Groves et al 1991) as well as other inflammatory sites (Bevilacqua et al 1994). The increased intensity of its expression in psoriatic skin compared with synovium found in the present study is similar to that previously reported by some (Veale et al 1995), but not others (Pitzalis et al 1996). Although the increased expression of E-selectin in skin may have a bearing on the greater expression of CLA on lymphocytes in skin, there was no significant correlation between E-selectin expression and the percentage of CLA positive lymphocytes. E selectin also binds neutrophils via the Sialyl Lewis X moiety, so its expression could reflect neutrophil diapedesis prominent in psoriatic skin but not synovium. In addition the reduction in mean vascular E-selectin intensity in psoriatic arthritis compared with rheumatoid arthritis was similar to that found previously (Veale D et al 1993). We have also studied E - selectin expression in osteoarthritis and found small quantities, similar to that found in the normal synovium of amputees (Fairburn et al 1993).

The CLA antigen is not specific to psoriasis but occurs in high percentage in normal and all inflammatory skin conditions (as we have found by studying normal skin and eczema). The remarkable similarity in the percentages of CLA positive lymphocytes

in all our patients also suggests that the molecule is not specific to psoriasis but is globally present on the majority of T lymphocytes in all skin, independent of the lymphocyte density. CLA is not present on virgin T cells but is up-regulated on a subset of T cells undergoing the virgin to memory transition in secondary lymphoid tissues (Picker et al 1993). Upregulation of CLA occurs in a highly regulated tissue-selective manner . For example, CLA is upregulated on over half of the T cells undergoing the virgin to memory transition in skin-associated peripheral lymph nodes but on fewer than 10% of transitional T cells in the mucosa of the small bowel. In addition CLA expression seems to be further up-regulated when memory-effector T cells are reactivated in skin, indicating that the local microenvironment at the time of T-cell activation acts to influence the homing receptor repertoire of the resultant memory-effector cells.

***Conclusions***

I conclude that the study supports the hypothesis that the CLA population of lymphocytes is essentially specific to skin, even when skin and an extra-cutaneous site of inflammation occur simultaneously in the same patient, as in psoriatic arthritis. Therefore there is no evidence to suggest that skin psoriasis and arthritis are linked through a common mechanism involving CLA T lymphocyte interactions with E-selectin. It remains possible that skin and joint disease in psoriatic arthritis could be linked through an undiscovered adhesion receptor for a particular T lymphocyte subset, or by a common T cell antigen. The topographic association of nail disease and distal interphalangeal joint disease still requires explanation, and examination of the distal interphalangeal joint and nailbed tissue itself may be the only way of determining related immunopathology. As skin disease usually precedes joint disease, knowledge of genetic susceptibility factors and mechanisms linking inflammation at separate sites may yet enable joint disease to be predicted and prevented.

# CHAPTER 4

# LIPOPROTEINS AND THEIR SUBFRACTIONS IN PSORIATIC ARTHRITIS : IDENTIFICATION OF AN ATHEROGENIC PROFILE WITH ACTIVE JOINT DISEASE

## SUMMARY

***Introduction.*** Dyslipoproteinaemia may be relevant in the management and ultimate outcome of patients with psoriatic arthritis.

***Hypothesis.*** Dislipoproteinaemia occurs in psoriatic arthritis and may be related to disease activity and atherogenic potential.

***Study Aims.*** (i) To characterise the lipid profile in psoriatic arthritis and investigate whether there are similarities to the dyslipoproteinaemia reported in rheumatoid arthritis and other inflammatory forms of joint disease. (ii) to investigate whether there is an atherogenic lipid profile in psoriatic arthritis, which may have a bearing on mortality.

***Study Design.*** Cross-sectional.

***Methods.*** Fasting lipids, lipoproteins and their subfractions were measured in 50 patients with psoriatic arthritis and their age and gender matched controls.

***Results.*** High density lipoprotein-cholesterol (HDL-cholesterol) and, specifically, its third subfraction, HDL-3-cholesterol, were significantly reduced in the psoriatic arthritis patients. The most dense subfraction of low density lipoprotein (LDL), LDL-3, was significantly increased in the psoriatic arthritis patients. Twenty patients with active synovitis had significantly lower total cholesterol, LDL-cholesterol and HDL-3-cholesterol than their controls. Twenty-five % of the psoriatic arthritis patients had elevated Lipoprotein (a) (Lp(a)) levels (> 300mg/l) compared with 19% of controls, athough this did not reach statistical significance.

***Conclusion.*** Elevated levels of LDL-3 combined with low levels of HDL-cholesterol are associated with coronary artery disease. We report such an atherogenic profile in a chronic inflammatory form of arthritis, which may be associated with accelerated mortality.

# INTRODUCTION

Metabolic factors may be of significance in the management and ultimate outcome of psoriatic arthritis patients. Patients with rheumatoid arthritis have an accelerated mortality compared with the general population, which may be attributed in part to an increased risk of cardiovascular disease (Pincus 1995). Active rheumatoid arthritis is associated with an abnormal lipid profile (dyslipidaemia). Altered concentrations of serum (London et al 1963, Rossner and Lofmark 1977, Lorber et al 1985, Lazarevic et al 1992, Svenson et al 1987), and synovial lipids (Winyard et al 1993) and lipoproteins may occur including a reduced serum cholesterol (London et al 1963), decreased serum triglycerides (Rossner and Lofmark 1977, Lorber et al 1985, Lazarevic et al 1992, Svenson et al 1987) and altered apoprotein concentrations (Rossner and Lofmark 1977). In addition decreased cholesterol in LDL, and cholesterol in HDL have been found, especially in association with active disease (Lorber et al 1985). The causes of mortality in psoriatic arthritis patients is less well documented, although there is evidence that psoriatic arthritis may be associated with an increased risk (Wong et al 1997). A pattern of dyslipoproteinaemia similar to that seen in rheumatoid arthritis has previously been reported in psoriatic arthritis, which normalises with a reduction in disease activity (Lazarevic et al 1992).

Routine plasma lipid measurement, which does not take account of lipoprotein composition may not identify patients with risk factors for atherosclerosis. Increased knowledge of lipoprotein composition and the identification of lipoprotein subfractions has added to our understanding of the mechanisms of metabolic disturbance in lipid disorders (Lindgren et al 1972). Detailed lipoprotein composition has not been previously measured in studies of arthritis. In population studies, a low HDL-cholesterol associated with a high LDL-cholesterol has been associated with an increased risk of atherosclerosis (Castelli et al 1986). The

smallest, most dense component of LDL, ( LDL-3), is the most important factor in contributing to atheroma (Austin et al 1988). Lipoprotein (a) (Lp(a)) has also emerged as an independent contributing factor to the risk of arteriosclerosis (Rosengren et al 1990, Terres et al 1995, Maher and Brown 1995). Increased levels of Lp(a) have been found in rheumatoid arthritis, but have not previously been measured in psoriatic arthritis (Rantapaa-Dahlqvist et al 1991).

The objectives of this study were firstly to characterise in detail lipoprotein composition, including Lp(a), in psoriatic arthritis and investigate whether there are similarities to the dyslipoproteinaemia reported in rheumatoid arthritis and other inflammatory forms of joint disease; secondly to investigate whether there is an atherogenic lipid profile in psoriatic arthritis, which may have a bearing on mortality.

# PATIENTS AND METHODS

### *Patients and Controls*

Fifty patients attending the psoriatic arthritis clinic at the Royal National Hospital for Rheumatic Diseases were studied. All patients had psoriasis, an inflammatory arthropathy and were sero-negative for rheumatoid factor. Age and gender matched controls were obtained from a concurrent local population survey and demographic details for both patients and controls are shown in Table 1. The exclusion criteria for patients and controls were diabetes, hypothyroidism, renal disease, alcoholism, current treatment with a lipid lowering agent, admission to hospital with a severe illness within the previous three months, pregnancy and breast feeding. Any other concurrent or previous illness known to affect the lipid profile (infection, malignancy, gout, ischaemic heart disease or liver disease) was recorded. Present and previous medication were noted for all patients with particular reference to oral corticosteroids, retinoids, thiazides, beta-blockers, oral contraceptives and hormone replacement therapy. Four patients in the control group had a history of gout but were not hyperuricaemic at the time of the study. All patients and controls were eating a normal Western diet. Body mass indices ($kg/m^2$) were calculated on all patients. Blood samples were taken from all patients after a 14 hour fast, centrifuged within two hours of collection and kept at $-20^0C$ until analysis. Samples for ultracentrifugation were analysed immediately.

### *Assessment of Disease Activity*

The inflammatory markers plasma viscosity, ESR and C-reactive protein (CRP) were measured in all patients. Active disease were defined as at least one clinically inflamed joint which was both swollen and tender. All of these patients had either an elevated ESR (>20 mm/hr) and/ or viscosity (>1.72mpas) and/or CRP (>0.01g/l) although this was not used to determine disease activity. The psoriasis area and

severity index (PASI) was used to document the severity and activity of skin disease (Camp 1992).

***Measurement of Lipoproteins***

Automated measurements were performed using an Abbott VP supersystem autoanalyser (Abbott Diagnostic Division, Maidenhead, UK). Lipids and lipoproteins were measured by standard precipitation techniques. Briefly, very low density lipoprotein (VLDL), total high density lipoprotein (HDL) and its third, most dense subfraction (HDL-3) were prepared by precipitation with sodium dodecyl suphate, Heparin-Manganese Chloride ($MnCl_2$) and dextran sulphate respectively. Cholesterol and triglyceride were measured in these subfractions by cholesterol oxidase para-amino-antipyrene (CHOD-PAP) and glycerol phosphate oxidase para-amino-antipyrene (GPO-PAP) enzymatic colorimetric methods (Boehringer , Mannheim, Germany) (inter-assay coefficients of variation (CV) 4% and 5%, and intra-assay CV 3% and 2% respectively). HDL-2 (density = 1.063-1.125g/ml) was calculated by subtraction of HDL-3 (density = 1.125-1.210g/ml) from total HDL. LDL- cholesterol and LDL- triglyceride were calculated by subtraction of the directly measured HDL and VLDL fractions from total serum cholesterol and triglyceride.

Apolipoprotein $A_1$ and apolipoprotein B were measured by electro-immunodiffusion in agarose gel (Sebia, Issy-les-Moulineaux, France). Lp(a) was measured in 45 patients by ELISA (TintElize Lp(a), Biopool, Sweden: Box 1454, S-901 24 Umea) (assay range 0-800 mg/l).

***Measurement of Lipoprotein Subfractions***

In 13 patients with active psoriatic arthritis from the total patient group and 13 age and gender-matched healthy volunteers, blood samples were fractionated by cumulative flotation ultracentrifugation based on the methodology described by

Lindgren et al (1972). Briefly, plasma was adjusted to a density of 1.118g/ml by adding solid sodium chloride (NaCl). Two mls of density adjusted plasma was layered onto the surface of 0.5 ml of a 1.182g/ml NaCl/sodium bromide density solution in an ultracentrifuge tube. The following density solutions were layered on the surface of the plasma: 1ml of 1.0988g/ml followed by 1ml of 1.086g/ml, 2ml of 1.079g/ml, 2ml of 1.0722g/ml, 1.5ml of 1.0641g/ml and finally 1.5ml of 1.0588g/ml. Ultracentrifugation was carried out in a SW41 Ti rotor at 23°C. Seven consecutive runs were performed, calculated to float lipoproteins of the following flotation rates (Sf = Svedberg flotation units) to the top of the tube:- Chylomicrons (Sf>400), three subfractions of very low density lipoprotein (VLDL) VLDL-1: Sf 100-400, VLDL-2: Sf 60-100, VLDL-3: Sf 20-60, and three subfractions of low density lipoprotein (LDL):- LDL-1: sf 12-20, LDL-2: sf 6-12, LDL-3: sf 3-6. After each run, chylomicrons, VLDL-1, 2 and 3 were aspirated from the top 0.5mls of the tube and LDL-1, 2 and 3 were aspirated from the top 1.0ml of the tube, and the tube refilled with the same amount of density solution (1.0588/ml). The cholesterol and triglyceride components of these subfractions were measured by the enzymatic colorimetric methods described above and automated measurements were made using the Abbott supersystem VP autoanalyser.

***Data analysis***

Data was entered onto an Apple Macintosh computer and analysed using Excel, Statworks and Multistat statistical packages. Paired t tests were used for continuous variables following normality testing and the $X^2$ test for comparing proportions. Prior to the analysis the non-normally distributed data including all triglyceride fractions and ratios and the VLDL-cholesteral: apolipoprotein B ratio, were logarithmically transformed for data analysis, and are given in the text and tables as antilogs. Values are presented as mean+/- standard error of the mean for normally distributed data or as antilogs (mean +/- standard error of the mean) for non-normally distributed data. The Mann-Whitney U test was used for the non-

parametric Lp(a) data. Pearson's coefficient of correlation was used for correlation analysis.

# RESULTS

### *Clinical Characteristics*

Fifty patients with psoriatic arthritis were recruited, 20 of whom met the criteria for clinically active peripheral joint disease. The patients spanned a spectrum of disease subgroups. All patients had mild skin disease only at the time of the study, and no patient had a PASI score greater than 10 (Table 1). The major difference in therapy between patients and controls was in the use of NSAIDs in all but two of the patients, which are not reported to affect lipid or lipoprotein levels. Psoriasis alone may affect serum lipid levels, although usually only when severe (Seishima et al 1994). There were no significant correlations between PASI scores and any lipid parameter.

### *Lipid and lipoprotein concentrations*

The lipid and lipoprotein results for 50 patients with psoriatic arthritis, including 20 patients with active joint disease, and their age and gender-matched controls are shown in Table 2. HDL-cholesterol was significantly reduced in the psoriatic arthritis patients and the difference was related to cholesterol in HDL-3. Reduced cholesterol levels were even more pronounced in the twenty patients with active synovitis who were analysed separately. Patients with active arthritis had significantly lower total cholesterol, LDL- cholesterol and HDL-3 - cholesterol than their controls. The relative overall influence of LDL - cholesterol and HDL - cholesterol was expressed by calculating the ratio of serum total cholesterol concentration to that of HDL- cholesterol (Table 2). The ratio tended to be higher for patients than controls in both the total patient group and those with active disease, but did not reach statistical significance.

To assess any proportional changes in cholesterol and triglyceride in patients versus controls, the ratios of total cholesterol to triglyceride and their relative proportions in

each lipoprotein were analysed (Table 2). For the total group of 50 patients, the cholesterol: triglyceride ratio in LDL was significantly less than in the control subjects, indicating a relative depletion of cholesterol compared with triglyceride in this lipopoprotein. There was a similar trend in patients with active arthritis although the difference did not reach sifnificance. The total cholesterol: total triglycerid ratio and proportions of cholesterol and triglyceride in HDL tended to be lower in the patient group, but the differences were not significant. The VLDL-cholesterol:VLDL-triglyceride ratio was similar for patients and controls.

***Apolipoproteins***

There were no significant differences in the apolipoproteins A1 and B in the psoriatic arthritis patients compared with controls for the total group (Table 2). In the 20 patients with active disease, both apolipoproteins tended to slightly lower but this was not significant. Apolipoprotein A1 is the predominant protein in HDL and apolipoprotein B the predominant protein in LDL. Therefore the apolipoprotein A1:HDL-cholesterol and apolipoprotein B:LDL-cholesterol ratios were calculated and compared for patients and controls. Both ratios tended to be greater for patients than controls, but in no case was this significant.

***Lipoprotein subfraction composition***

Thirteen patients with active joint disease were further studied for lipoprotein subfraction composition. Their initial profiles were similar to the 20 patients with active disease (data not shown). HDL-cholesterol was again significantly reduced compared with controls (1.09 v 1.41 mmol/l; $p<0.005$).

On analysing LDL subfraction constituents (Table 3) the major difference between psoriatic arthritis patients and controls was an increase in all components of LDL-3. There were significantly greater concentrations of total cholestererol, in both its free and esterified forms, triglyceride, phospholipid and protein in LDL-3. Thus the total

mass of LDL (lipid + protein) and LDL-3:total LDL mass ratio was significantly greater in psoriatic arthritis compared with controls (Table 3) and there was a greater percentage of LDL -3 in total LDL in psoriatic arthritis (24.8%) compared with controls (15.5%)(t-test, $p < 0.001$).

We next analysed the proportions of the various components making up the LDL lipoprotein subfractions (Figure 1). All components within LDL-3 were uniformly increased with no disproportion compared to controls, apart from an increase in phospholipids. However, there was significantly less cholesterol in LDL-1 and LDL-2 in patients compared with controls and a concomitant greater percentage of triglyceride in LDL-2 (Figure 1).

There were no significant differences between patients and controls in the total mass of VLDL-1, VLDL-2 or VLDL-3 subfractions or in the concentration of their constituents, but there are some significant differences in the percentage composition of the various constituents (Figure 2). There was a trend for the triglyceride, cholesterol and phospholipid concentrations in VLDL-1 and its total mass to be increased compared with controls (Table 3). The mean proportion of VLDL-1 in total VLDL was 22.3% versus 16.5% for controls . Also, the percentage of triglyceride in VLDL-3 was significantly reduced in the patients compared with controls and there was a trend for an increase in the percentage of triglyceride in VLDL-1 (Figure 2).

The chylomicron phospholipid concentration was significantly less in psoriatic arthritis compared with controls (Table 3) which was reflected in a significant decrease in the percentage composition of phospholipid in chlyomicrons (Figure 2).

***Lipoprotein (a)***

There were no significant differences in Lp(a) levels in patients with psoriatic arthritis and controls (median 174 mg/l (range 10 - 800) v 157mg/l (range 10 - 800)). When the patients with active synovitis were analysed separately, Lp(a) levels was found to be increased (median 187 mg/l v 88 mg/l) but this did not reach statistical significance (Mann Whitney U test). Also, 25% of psoriatic arthritis patients had Lp(a) levels greater than 300mg/l compared with 19% of the controls although the difference in the proportion was not significantly different. A power calculation indicates that 360 patients and controls would be required to gain a significant difference in the proportion of patients and controls with an Lp(a) of greater than 300mg/l. There were weak positive correlations between Lp(a) levels and ESR (Pearson's r=0.27, p=0.098), plasma viscosity (r=0.27) and CRP (r=0.18).

***Conclusions.***

The major findings of this study are as follows. High density lipoprotein-cholesterol (HDL-cholesterol) and, specifically, its third subfraction, HDL-3-cholesterol, were significantly reduced in the psoriatic arthritis patients. The most dense subfraction of low density lipoprotein (LDL), LDL-3, was significantly increased in the psoriatic arthritis patients. Twenty patients with active synovitis had significantly lower total cholesterol, LDL-cholesterol and HDL-3-cholesterol than their controls. Twenty-five % of the psoriatic arthritis patients had elevated Lipoprotein (a) (Lp(a)) levels (> 300mg/l) compared with 19% of controls, athough this did not reach statistical significance.

**TABLE 1. Clinical Details of 50 patients and controls with specific reference to factors known to affect lipids.**

| Factor | | Patient | Control |
|---|---|---|---|
| Mean Age (years/range) | | 44.8 (20-72) | 44.8 (20-72) |
| Sex (M/F) | | 21/29 | 21/29 |
| Mean Body Mass Index (SD) | | 25.8 (5.6) | 24.6 (4.7) |
| PASI Score (Mean/range) | | 3.3 (0-8.7) | 0 |
| Subgroup of Joint Disease (No. of Patients) | | | |
| | Oligoarthritis | 21 | 0 |
| | Polyarthritis | 27 | 0 |
| | Mutilans | 1 | 0 |
| | Spondylitis | 1 | 0 |
| HIstory of Gout | | 0 | 4 |
| Topical dovanex | | 1 | 0 |
| NSAIDs | | 48 | 0 |
| Oral Contraceptive | | 0 | 5 |
| Hormone replacement therapy | | 0 | 7 |
| Anti-hypertensives | | | |
| | Beta-blockers | 1 | 1 |
| | Thiazides | 1 | 1 |

No patient or control had concurrent infection, malignancy, ischaemic heart disease, liver disease or was taking corticosteroids or retinoids.

**TABLE 2. Lipid and lipoprotein concentrations in 50 psoriatic arthritis patients and 20 patients with active diseases and their age and sex matched controls.**

Results expressed as mean (SEM); Statistics: t-test

| Lipid/Lipoprotein Concentration(units) | Psoriatic Arthritis Patients (N=50) | Controls | Patients with Active Disease (N=20) | Controls |
|---|---|---|---|---|
| Mean Age/years (range) | 44.8 (20-72) | 44.8 (20-72) | 42.5 (20-72) | 42.5 (20-72) |
| Total Cholesterol (mmol/L) | 5.43 (0.2) | 5.82 (0.13) | 4.99 (0.24)*** | 6.08 (0.22)*** |
| VLDL-Cholesterol (mmol/L) | 0.51 (0.05) | 0.49 (0.04) | 0.44 (0.05) | 0.51 (0.04) |
| LDL-Cholesterol (mmol/L) | 3.67 (0.19) | 4.0 (0.1) | 3.3 (0.25)* | 4.12 (0.25)* |
| HDL-Cholesterol (mmol/L) | 1.12 (0.05)* | 1.29 (0.1)* | 1.09 (0.05) | 1.33 (0.1) |
| HDL-3 Cholesterol (mmol/L) | 0.62 (0.04)*** | 0.75 (0 .02)*** | 0.62 (0.1)* | 0.77 (0.09)* |
| HDL-2 Cholesterol (mmol/L) | 0.52 (0.03) | 0.57 (0.04) | 0.49 (0.18) | 0.56 (0.17) |
| Total Cholesterol: HDL Cholesterol | 5.40 (0.34) | 5.14 (0.47) | 5.30 (0.65) | 4.86 (0.33) |
| Total Triglyceride (mmol/L) | 1.15 (1.09) | 1.13 (1.07) | 0.99 (1.14) | 1.35 (1.1) |
| VLDL-Triglyceride (mmol/L) | 0.30 (1.15) | 0.32 (1.13) | 0.25 (1.22) | 0.35 (1.27) |
| LDL-Triglyceride (mmol/L | 0.63 (1.1) | 0.52 (1.1) | 0.53 (1.16) | 0.59 (1.13) |
| HDL-Triglyceride (mmol/L) | 0.23 (1.04) | 0.25 (1.15) | 0.21 (1.06) | 0.24 (1.11) |
| Total Cholesterol: Total Triglyceride | 4.57 (1.07) | 5.00 (1.07) | 4.95 (1.65) | 4.44 (1.51) |
| VLDL-Cholesterol: VLDL-Triglyceride | 1.35 (1.07) | 1.36 (1.07) | 1.36 (1.65) | 1.23 (1.84) |
| LDL-Cholesterol: LDL-Triglyceride | 5.47 (2.23)** | 7.40 (1.07)** | 5.75 (1.86) | 6.69 (1.49) |
| HDL-Cholesterol: HDL-Triglyceride | 4.76 (1.05) | 4.95 (1.20) | 4.71 (1.54) | 5.26 (1.55) |
| Apolipoprotein A1 (mg/dl) | 137 (4.22) | 137 (4.88) | 134 (4.22) | 145 (4.88) |
| Apolipoprotein B (mg/dl) | 80 (3.68) | 78 (5.86) | 71 (3.68) | 83 (5.86) |
| Apolipoprotein A1 : HDL-C | 132 (6.8) | 115 (6.2) | 138 (16.7) | 111 (4.16) |
| Apolipoprotein B : LDL-C | 24 (2.2) | 19.9 (0 .92) | 25 (4.68) | 21 (1.12) |

Significant results for psoriatic arthritis patients versus controls:
* $p<0.05$; ** $p<0.01$; *** $p<0.005$.

## TABLE 3. Concentration of cholesterol, triglyceride, phospoholipid and protein of each lipoprotein subfraction and their total mass for patients with psoriatic arthritis and controls (N=13).

Results expressed as mean (SEM); Units
mg/dl

| | Total Cholesterol | | Triglyceride | | Phospholipid | | Protein | | Total mass | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Patient | Control | Patient | Control | Patient | Control | Patient | Control | Patient | Control |
| Chylomicrons | 0.12 (0.03) | 0.11(0.02) | 0.36 (0.13) | 0.45 (0.14) | 0.05 (0.01)* | 0.37 (0.15)* | 0.18 (0.03) | 0.35 (0.18) | 0.65 (0.16) | 1.28 (0.29) |
| VLDL-1 | 1.82 (0.59) | 1.05 (0.27) | 14.5 (4.44) | 7.62 (1.48) | 2.8 (0.9) | 1.06 (0.2) | 1.81 (0.59) | 1.19 (0.32) | 20.94 (6.49) | 10.92 (1.99) |
| VLDL - 2 | 3.09 (1.05) | 2.08 (0.41) | 15.5 (4.48) | 11.62 (2.09) | 4.2 (1.3) | 2.46 (0.33) | 2.99 (0.89) | 2.1 (0.34) | 30.65 (18.35) | 12.38 (3.03) |
| VLDL - 3 | 9.67 (2.66) | 7.79 (1.43) | 20.88 (4.83) | 16.38 (1.94) | 9.89 (2.37) | 7.03 (1.05) | 7.0(1.88) | 6.0(0.85) | 45.22 (12.04) | 35.52 (3.96) |
| LDL - 1 | 13.95 (1.85) | 15.24 (1.86) | 9.49 (1.15) | 7.68 (0.81) | 9.99 (1.12) | 9.12 (1.25) | 9.56 (0.9) | 9.03 (0.97) | 42.99 (4.51) | 41 (4.51) |
| LDL - 2 | 55.92 (2.99) | 65.96 (4.92) | 10.77 (1.33) | 8.48 (1.03) | 34.49 (3.17) | 37.59 (2.95) | 39.95 (1.96) | 40.99 (2.66) | 142.8 (9.46) | 153.6 (9.97) |
| LDL - 3 | 25.59 (3.81)** | 14.53 (0.79)** | 4.02 (0.67)** | 1.92 (0.23)** | 13.98 (3.39)* | 7.28 (0.72)* | 20.74 (3.42)* | 11.92 (0.91)* | 61.9 (10.61)* | 35.65 (2.18)* |

Significant results for psoriatic arthritis patients v controls:
* $p < 0.05$; ** $p<0.01$

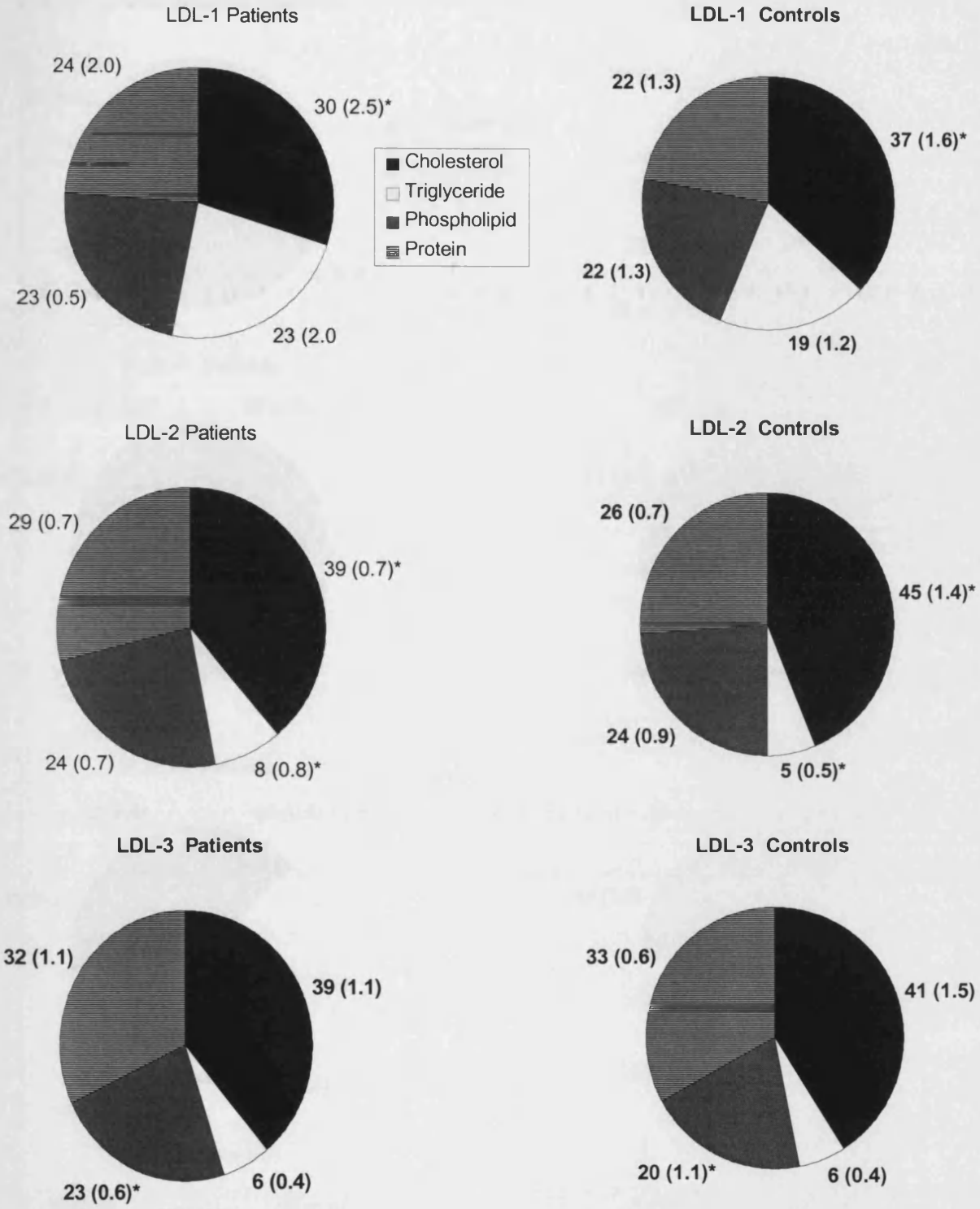



**Figure 1. Percentage composition of cholesterol, triglyceride, phospholipid and protein in LDL for patients with psoriatic arthritis and controls.**

Results given as mean (SEM); * denotes significant result.

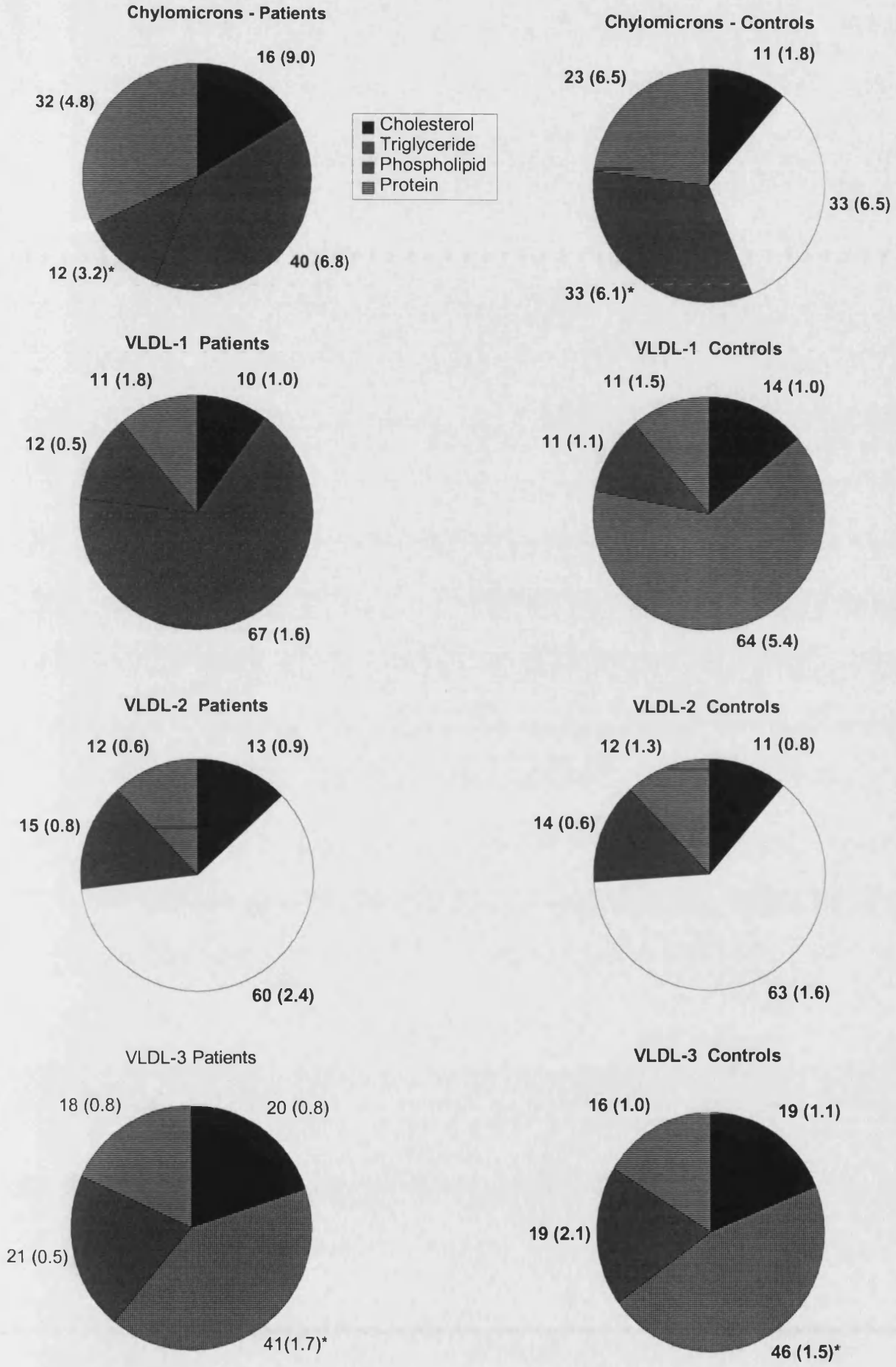



**Figure 2. Percentage composition of cholesterol, triglyceride, phospholipid and protein in chylomicrons and VLDL for patients with psoriatic arthritis and controls.**

Results given as mean (SEM); * denotes significant result.

## DISCUSSION

A pattern of dyslipidaemia similar to that found in rheumatoid arthritis has been reported in patients with psoriatic arthritis. Lazarevic et al (1992) studied 40 patients with psoriatic arthritis and found decreased concentrations of total lipids, total cholesterol, cholesterol in LDL, and cholesterol in HDL which normalized with a reduction in disease activity. In our current study, we have also found significantly reduced total cholesterol, LDL- cholesterol and HDL- cholesterol and the generalised supression of total cholesterol, LDL and HDL cholesterol was most apparent in those patients with active joint disease. In addition there was a significant elevation of LDL-3 total mass and its cholesterol and triglyceride components, and a tendency for Lp(a) to be increased. Neither of the lipid particles LDL-3 or Lp(a) have been previously studied in psoriatic arthritis.

A decrease in total LDL-cholesterol observed in our study group may imply protection from atherosclerosis. However, patients with active psoriatic arthritis had a significant shift in distribution towards the smallest, most dense particles of LDL (LDL-3), with normal or low levels of LDL-1 and LDL-2. LDL-3 constituted 24.8% of total LDL compared with 15% of controls. These findings have clinical relevance because high levels of LDL-3 in relation to LDL-1 and LDL-2 are strongly associated with atherosclerosis in population studies (Austin et al 1988). A similar pattern has been reported in non-insulin dependent diabetes mellitis in which LDL-cholesterol may be normal or reduced in association with excess small dense LDL-3 and low HDL-cholesterol (James et al 1994, Barrett-Connor et al 1983). The shift in LDL composition is much more marked in diabetes mellitis where the percentage of LDL-3 in total LDL may reach 40%. In diabetes the shift is associated with hypertriglyceridaemia and increased VLDL-1. High levels of VLDL-1 may be more slowly catabolised, particularly if there is reduced lipoprotein lipase activity. High levels of VLDL-1 encourages increased neutral lipid transfer of cholesterol ester

from HDL and LDL to VLDL, in exchange for triglyceride, leading to small dense LDL (LDL-3). In the current study, there were no significant differences in the total triglyceride levels or the concentration of VLDL subfractions compared with controls; however there was a trend for a slightly greater proportion of VLDL-1 in relation to VLDL-2 and 3 which suggests that the postulated mechanism in diabetes may be operating to some extent in active psoriatic arthritis.

The combination of a low HDL-cholesterol and a high LDL-3 found in the current study is strongly associated with an increased risk of atherosclerosis in population studies (Regnstron et al 1992). There are a number of mechanisms whereby increased LDL-3 may cause atherosclerosis. LDL-3 becomes rapidly oxidised and has an enhanced ability to cross cell surfaces where it may be directly toxic to endothelium. The clearance of LDL-3 from the circulation by the LDL receptor mechanism may also be impaired making more LDL available for removal by the atherogenic scavenger pathway (Nigon et al 1992). In the arterial wall, the resulting lipid-rich macrophages become foam cells that accumulate in early atheromatous lesions. An association between the susceptibility of low-density lipoproteins to oxidation in vitro and the extent of atherosclerosis of coronary vessels has been demonstrated (Campos et al 1992).

Lp(a) is an independent risk factor for atherosclerosis and thrombosis with values above 300mg/l associated with a twofold increased risk of myocardial infarction (Rosengren et al 1990) and an accelerated progression of coronary atheroma (Terres et al 1995). Its mode of action is thought to be related to homology with plasminogen resulting in inhibition of fibrinolytic activity and increasing the likelihood of thrombosis. Increased levels of Lp(a) have been reported in rheumatoid arthritis, where it may behave as an an acute phase protein (Maher and Browm 1995). Our results show a similar pattern with a slight increase in Lp(a) levels and

weak positive correlations with inflammatory markers, although none of the differences reached statistical significance.

Lipoproteins exist as packages containing predominantly cholesterol, triglyceride and apolipoproteins. The synthesis and catabolism of each constituent can proceed independently of the other contents of the package, although a certain amount of covariance exists. LDL cholesterol and triglyceride may be high or low, without any change or with an opposing change in apolipoprotein concentration. Apolipoprotein A1 is the predominant apolipoprotein in HDL, constituting 60% of the protein mass, and apolipoprotein B the predominant apolipoprotein in LDL and VLDL, constituting 90% of the protein mass of LDL. LDL and VLDL have one apolipoprotein per lipoprotein package, so apolipoprotein concentration is an indication of the number of particles present. Lower apolipoprotein A1 and high apolipoprotein B have been found in association with coronary artery disease. The apolipoproteins apo A1 and apo B in the psoriatic arthritis patients were not significantly different from controls, although they tended to be lower in the active group, perhaps partly reflecting the generalized reduction in cholesterol and cholesterol-associated lipids. This notion is supported by the apolipoprotein A1: HDL-cholesterol and apolipoprotein B: LDL-cholesterol ratios which tended to be greater in the patients than controls, reflecting a greater relative suppression of HDL-cholesterol than apolipoprotein A1 and LDL-cholesterol than apolipoprotein B.

There are a number of reasons why dyslipidaemia may be associated with an active inflammatory arthritis. An increased production of acute-phase proteins by the liver in inflammation may occur at the expense of lipoprotein production, thereby tending to reduce lipoprotein levels (London et al 1963). Enhanced reticulo-endothelial system uptake of lipoproteins in chronic inflammation may occur, which is compatible with an accelerated atherosclerotic process at the vessel wall (Svenson et

al 1987). Mediators of inflammation, such as the interferons ($\alpha,\beta,\chi$) , C-reactive protein and the pro-inflammatory cytokines interleukin 1 and TNF$\alpha$ produced by macrophages have been shown to suppress lipoprotein lipase activity and increase oxidative metabolism (Ilowite et al 1988, Ogawa et al 1989, Spriggs et al 1988, Fried et al 1989, Beutler and Cerami 1985, Rosenzweig et al 1987, Rowe et al 1984). Reduced levels of the anti-oxidant selenium has also been found in psoriatic arthritis (Azzini et al 1995).

The increased suppression of HDL-3 in relation to HDL-2 and total HDL also requires explanation. The triglyceride-rich HDL-2 is converted to the smaller lipoprotein HDL-3 by hepatic triglyceride lipase in the endothelium of hepatic sinusoids. Hepatic lipase may be suppressed, possibly by the effects of pro-inflammatory cytokines, in active psoriatic arthritis. It is likely that a combination of factors related to the systemic inflammatory response may operate in psoriatic arthritis to produce the observed pattern of dyspipoproteinaemia.

A reported increase in occlusive vascular disease in psoriasis has lead to various studies of lipids and lipoproteins, with conflicting results (Seishima et al 1994). Hypercholesterolaemia and/or hypertriglyceridaemia may occur which contrasts with the findings in psoriatic arthropathy. Apoliopoprotein B has been reported to be low, unchanged or increased in different studies (Seishima et al 1994, Brustein et al 1976). However an increased prevalence of hypertension, diabetes mellitis, impaired glucose tolerance and hyperuricaemia, all of which are known to be associated with dyslipoproteinaemia, are associated with psoriasis and may not have been adequately controlled in some studies. In addition the severity of psoriasis may affect the results (Seishima et al 1994). None of our patients had severe skin disease (defined as a PASI score of greater than 30) at the time of the study, making it unlikely that psoriasis per se contributed to our findings.

***Conclusions***

To conclude, this is the first report documenting high levels of LDL-3 in relation to total LDL in a chronic inflammatory form of arthritis. Lipoprotein composition warrants further investigation in rheumatoid arthritis where the increased mortality from atherosclerosis is more clearly established. In patients with the pattern of low HDL, high LDL-3 and high Lp(a), long term follow up is needed to determine the predictive risk of macrovascular disease.

# CHAPTER 5

# GENERAL DISCUSSION

Classification of disease should differentiate and completely describe the spectrum of all clinical patterns. None may be universally satisfactory, because every proposal derives from studies in locally selected populations. The natural history of the disease (eg genetic, environmental, geographic) are dissimilar in different populations. The recognition of new subsets should be supported by their different genetic or clinical features or by their distinctive prognosis. The perplexities of subgroup classification in psoriatic arthritis was discussed in detail in Chapters 2a and b and is well recognised in a recent review (Oriente, Biondi Oriente and Scarpa 1994). The debate regarding the most appropriate method to use continues (Scarpa et al 1997).

I divided our patients into six subgroups, based on Moll and Wright's original classification. This remains widely used by clinicians, and continues to be taught to students, despite many attempts to gain universal agreement on more homogeneous subgroups (Veale et al 1994). The subgroups used in Chapters 2a and b were as follows - monoarthritis, DIP joint disease alone, oligoarthritis, polyarthritis, spondyloarthritis and arthritis mutilans. The following criticisms can be directed at this classification. Firstly, monoarthritis and oligoarthritis, when strictly defined by the number of joints involved, may represent an earlier point in the time-course of disease than polyarthritis, and may evolve to polyarthritis (Chapters 2a and b). To increase subgroup homogeneity, 'oligoarthritis' could be loosely defined as 'fewer joint involved than would be expected in rheumatoid arthritis' in association with typical features of psoriatic arthritis such as dactylitis and enthesopathies. Polyarthritis should be interpreted as involving many joints, either in association with 'typical features of psoriatic arthritis' or in a pattern indistinguishable from

rheumatoid arthritis. Secondly, both distal interphalangeal joint disease and spondyloarthritis may occur in the other subgroups of peripheral joint disease (Chapter 2a, Veale et al 1994). Thirdly, arthritis mutilans is also a severe form of polyarthritis and the key radiographic and pathological finding in this condition, osteolysis, may occur in more limited disease involving single joints or a few joints only. Lastly, the full spectrum of disease in psoriatic arthritis and in particular the associated extra-articular abnormalities may not be covered by these subgroups of joint disease. Extra-articular osseous abnormalities were found to be sufficiently common by radionucleotide scanning to justify a separate subgroup by Helliwell et al (1991) and osteoperiostitis of the great toe has recently been described (Goupille et al 1996).

The definition of psoriatic arthritis is important when considering recent proposals for further subgroups. Isolated peripheral enthesitis and /or dactylitis has been described as a subset of psoriatic arthritis (Salvarani et al 1997). However, the patients were seen over a six month period only, and longer follow-up would be required to assess whether joint involvement ultimately occurred. One of our patients had isolated dactlyitis of the toes at five year follow-up which begs the question of whether she was correctly included in the oligoarthritis subgroup when first seen in the clinic, ie were the joints or just soft tissue structures involved. Strictly speaking, patients with isolated dactylitis do not have an inflammatory arthropathy, so would not meet the Moll and Wright criteria for diagnosis, although many clinicians would make the diagnosis of psoriatic arthritis in such patients .

It may be difficult to determine whether joints underlying severe dactlylitis are involved as the whole digit may be painful and joint movement may be painful and restricted. The structures involved in dactylitis in psoriatic arthritis and other spondyloarthropathies has been recently assessed by two groups using magnetic resonance imaging and ultrasonography with conflicting results (Olivieri et al 1997;

Kane et al 1997). Olivieri et al assessed toe dactylitis in seven patients and found flexor, and less frequently, extensor tenosynovitis. Capsular distension of the joints was used as a marker of joint involvement and was uncommon. It occurred in two MTP joints only. In a similar study, Kane et al found articular involvement to be common, occurring in 56% of patients (Kane et al 1997).

Another recent study has distinguished the arthritis associated with pustular psoriasis and psoriatic arthritis (Mejjad O et al 1996) and found anterior chest wall involvement to be common, and fewer joints involved. This particular pattern of skin disease was rare, occurring in only three of the patients (Chapter 2a and b). One of these had chest wall involvement, oligoarthritis and SAPHO (Benhamou et al 1988). No other association between the type or severity of psoriasis and a specific pattern of joint disease was observed in the studies presented (Chapters 2a, b to c)

Other extra-articular sequelae may occur in psoriatic arthritis. One of the patients reported in Chapter 2a and b developed a myelopathy related to neck disease, a complication recognised in psoriatic arthritis and recently reported (Agaki et al 1996, Sosner et al 1996). Other potentially serious extra-articular complications that have been reported, but were not diagnosed in our series include pyoderma gangrenosum and secondary amyloid, which has been reported as causing the death of a patient with arthritis mutilans (Tsuda et al 1996; Ahmed et al 1996, Smith and White 1994; Klunemann et al 1994).

Subgroups should, if possible, be homogeneous with time. The studies presented in Chapters 2a and b clearly indicate that subgroups strictly defined on the basis of the number of joints involved (oligoarthritis and polyarthritis) evolve from mono- or oligoarthritis to polyarthritis, and polyarthritis to mutilans as the disease progresses. This evolution of disease subgroups, with deterioration of joint disease over time is gaining wider acceptance (Espinoza and Cuéllar, 1998). It has also been recognised

that some patients may have a benign cause with an initial presentation which subsides never to recur. Gladman has also reported complete resolution in 7 patients. This was the case in 4% of our patients , who had no evidence of joint involvement at follow-up. A set of prognostic indicators is required, so that patients most likely to progress are identified and appropriately treated. This issue has been evaluated in detail by Gladman et al (1995) who devised a univariate and multivariate risk model for disease progression. One of the most striking clinical features in both models is that a low sedimentation rate protects against disease progression. The correlation of the baseline viscosity with the rate of progression of joint disease in Chapter 2b supports this finding, and suggests that attempts should be made to suppress inflammation early in the course of the disease.

The presence of elevated inflammatory markers may be associated with other metabolic extra-articular effects, and may even affect cardiovascular mortality (Chapter 2b and 4). In the study presented in Chapter 4 dyslipoproteinaemia was found in patients with active disease. This included a reduced HDL and high LDL-3, which has been related to an increased risk of cardiovascular disease in population studies (Austin et al 1988, Regnstron et al 1992). A prospective epidemiological study is required to substantiate this.

Nail disease has been consistently found to be increased in patients with psoriatic arthritis versus those with psoriasis alone, and may be a susceptibility factor for the development of arthritis (Gladman et al 1986). It is of interest that eleven further patients had evidence of nail disease at follow-up, with a total percentage of 78% (Chapter 2b) and that 87% of the patients included in Chapter 2c had nail disease by the end of the study. The association of DIP joint disease with nail disease in the same digit has long been recognised (Bauer et al 1941). The study presented in Chapter 2a is the first to demonstrate this statistically (Jones et al 1994). A recent larger study has confirmed this finding (Kay et al 1997). A variant of psoriatic distal

inerphalangeal arthritis has recently been described - psoriatic onycho-pachydermo-periostitis (Boisseasu-Garsaud et al 1996).

The periodicity or temporal relationship was assessed prospectively for the first time in Chapter 2c. A consistent temporal relationship between exacerbations and remissions of skin and joint disaese, skin and nail disease and joint and nail disease was found in only a minority of patients. This characteristic did not define a subset of joint disease or suggest a specific prognosis.

The relationship of the rheumatoid arthritis HLA DRB1 'shared epitope' to susceptibility, severity and progression of psoriatic arthritis was assessed in Chapter 2d. No significant increases in the prevalence of the 'shared epitope' was found in psoriatic arthritis versus controls and it was concluded that the 'shared epitope' does not significantly influence the susceptibility to psoriatic arthritis or the severity of disease in sero-negative patients. The lack of association with the SE and psoriatic arthritis is further evidence of its separate identity from rheumatoid arthritis. The under-representation of DR4 and specifically the *0401 allele compared with controls suggests that other HLA-DRB1 alleles may have greater importance, such as DR7. This allele has consistently been found to be increased in studies of psoriatic arthritis (McHugh et al 1987, Eastmond 1994). However, it is also strikingly over-represented in psoriasis alone. It has been suggested that DR7 may act as a protective factor for the development of arthritis (Gladman 1995a).

A possible immunological explanation for the link between skin and joint disease in psoriatic arthritis was evaluated in Chapter three. The T lymphocytic infiltrate of psoriatic skin and inflamed synovium was examined for the presence of cutaneous lymphocyte antigen (CLA) positive cells that are known to occur in large numbers in inflamed skin. The data supported previous evidence that the CLA molecule is enriched only on skin-homing T lymphocytes (Picker et al 1990), similar to the

results reported in another recent study of psoriatic arthritis (Pitzalis et al 1996). Differential expression of the CLA antigen represents the single most prominent difference between the T lymphocyte infiltrate in psoriatic skin and synovium.

Differences in the T lymphocyte infiltrate may be consistent with existing observations regarding the link between psoriasis and arthritis. For instance there is no association between the type or distribution of skin involvement and arthritis subgroup (Jones et al 1994 and Chapter 2a and b). Also, a pattern of joint disease typical of mutilating psoriatic arthritis may occur without skin disease or with nail disease only (O'Neill et al 1992). In the majority of patients the skin disease presents first and although up to 35% of patients report exacerbations of both skin and peripheral joint disease joint disease, this temporal relationship only occurs slightly more often than would be expected by chance (Gladman et al 1987, Chapters 2b and c).

# CONCLUSIONS AND FUTURE WORK

***Outcome***

This Thesis demonstates that psoriatic arthritis is a heterogeneous disease in onset, expression and outcome. The arthritis may vary considerably in its pattern and has been divided into several subgroups (Moll and Wright 1973, Chapters 2a and b). It was once considered a benign disease. This has been shown to be a fallacy. Polyarthritis is most common in patients referred to rheumatologists (Chapters 2a and b, Wright 1992, Jones et al, 1994) and the majority of patients have progressive peripheral joint disease (Gladman et al 1995, Chapter 2b). Radiological damage in the hand is progressive in the majority of patients with psoriatic arthritis, especially those with widespread damage at baseline.

One of the problems in studying the disease is the lack of agreement between researchers on its definition and classification, and different interpretations resulting in apparently conflicting clinical data. This needs to be resolved urgently, and a formal epidemiological study lead by Deborah Symmons, (epidemiologist and Reader in Rheumatology at Manchester University) has been initiated to formally resolve this issue. The study will base its criteria for diagnosis on a concensus of opinion by International rheumatologists with an interest in psoriatic arthritis, and then formally evaluate the criteria by a prospective clinical study.

Mortality of disease in relation to the population is a vital outcome measure and the largest study has recently been published by Gladman's group which had sufficient patients and controls to provide cause-specific standardised mortality ratios. This needs to be confirmed by British data of similar quality and quantity.

*Link Between Skin, Joint and Nail Disease*

This Thesis shows that skin psoriasis and arthritis are not linked through a common mechanism involving CLA T lymphocyte interactions with E-selectin. This may instead be an important important immunological difference between the skin and joints in the disease. It remains possible that skin and joint disease in psoriatic arthritis could be linked through an undiscovered adhesion receptor for a particular T lymphocyte subset, or by a common T cell antigen.

The topographic association of nail disease and distal interphalangeal joint disease still requires explanation, and examination of the distal interphalangeal joint and nailbed tissue itself may be the only way of determining related immunopathology. Abnormalities of blood vessels, both qualititative and quantitative, may provide an explanation for the link between the nail and the adjacent DIP joints. Capillaroscpy is a useful clinical tool for examining this. The appearances of the vessels of the nail bed in affected and unaffected nails in patients with and without DIP joint disease or dactylitis could be compared. This clinical study could be linked to a study promoters and inhibitors of angiogenesis, the dysregulation of which may provide an explanation for the link.

*Immunogenetics*

The HLA system is likely to be functionally important in the initiation and perpetuation of inflammation in psoriatic arthritis. Study of linked polymorphisms with well-defined functions, such as TNFα is potentially exciting and may have direct implications for treatment (Al-Heresh et al 1997). The relative contribution of the HLA and identification of other candidate genes which may determine susceptibility and severity is currently being assessed by linkage studies in AS and RA. This would be a complex undertaking in psoriatic arthritis because of disease heterogeneity, and the presence of psoriasis. Some patients with psoriatic spondyloarthropathy are likely to be included in studies of ankylosing spondylitis

and patients with rheumatoid arthritis and coincident psoriasis may be included in studies of rheumatoid arthritis. However, specific studies in psoriatic arthritis are required if a reliable genetic prognostic risk model is to evolve. This would require tightly defined diagnostic and classification criteria and a multicentre approach. As skin disease usually precedes joint disease, knowledge of genetic susceptibility factors in combination with mechanisms linking inflammation at separate sites may yet enable joint disease to be predicted and prevented.

***Quality of Life Measures***

Psoriatic arthritis has a complex impact on a patient's social functioning, disability and handicap. This impact is dependent on the activity and severity of both joint and skin disease. Although skin disease may not correlate closely with joint disease, and each may require separate triggers for their expression, an index encompassing both manifestations may be useful in determining the overall impact of the disease. It may also be useful in assessing the total response to therapeutic agents such as methotrexate and cyclosporin that may benefit both manifestations of the disease.

***Therapy***

The unpredictability of the course of peripheral disease and response to therapy in psoriatic arthritis is of major concern to both patient and rheumatologist. Patients need continuous access to multidisciplinary care, as well as appropriate early disease modifiying therapy. Good prognostic indicators are essential in justifying early intervention. Patients with psoriatic arthritis should be included in properly designed prospective therapeutic trials of single agents or combinations of agents to assess their efficacy and safely, and included in trials of new immuno-active agents.

## REFERENCES

1. Abu-Shakra M, Gladman DD, Thorne JC, Long J, Gough J, Farewell VT. Longterm methotrexate therapy in psoriatic arthritis: Clinical and radiological outcome. *Journal of Rheumatology* 1995;22:241-245.

2. Agaki S, Saito T, Dato I, Ogawa R. Cervical myelopathy in psoriatic spondylitis . *Scand J Rheumatol* 1996;25 (5):337-339.

3. Al-Jarallah KF, Singal DP, Buchanan WW. Immunogenetics of psoriatic arthritis. *Immunological Investigations* 1993;22 (2):81-86.

4. Alenius GM, Sojka BN, Nordmark L, Nordstrom S, Rantapaa Dahlquist S. A multicase family with spondyloarthropathies. *Scandinavian Journal of Rheumatology* 1997;26;2:107-112.

5. Alibert JL. *Precis Theoretique et Pratique sur les Maladies de la Peau.* Paris: Caille de Ravier, 1822.

6. Armstrong RD, Panayi GS, Welch KI. Histocompatibility Antigens in Psoriasis, Psoriatic Arthritis and Ankylosing Spondylitis. *Annals of the Rheumatic Diseases* 1983;42:142-146.

7. Arnett FC. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis and Rheumatism* 1988;31:315-324.

8. Arnett FC, Revielle JD, Duvic M. *Psoriasis and psoriatic arthritis associated with HIV infection*. Philadelphia: Saunders, 1991.

9. Austin MA, Breslow JC, Hennekens CH, Buring JE, Willett WC, Kraus RM. LDL subclass pattern and risk of myocardial infarction. *Journal of the American Medical Association* 1988;260:1917-1921.

10. Avila R, Pugh DG, Slocomb CH, WInkleman RK. Psoriatic arthritis: a roentgenographic study. *Radiology* 1960;75:691-701.

11. Azzini M, Girelli D, Olivieri O, et al. Fatty acids and antioxidant micronutrients in psoriatic arthritis. *Journal of Rheumatology* 1995;22:103-108.

12. Baker H. *The relationship between psoriasis, psoriatic arthritis and rheumatoid arthritis. An epidemiological, clinical and serological study*. University of Leeds: MD Thesis, 1965.

13. Barker JNWN. The immunopathology of psoriasis. In: Wright V, Helliwell P, eds. *Bailliere's Clinical Rheumatology: Psoriatic Arthritis*. London: Bailliere Tindall, 1994. p.429.

14. Barraclough D, Russell AS, Percy JS. Psoriatic Sponsylitis: a clinical, radiological and scintiscan survey. *Journal of Rheumatology* 1977;4:282.

15. Barrett-Connor E, Witztum JL, Holdbrook M. A community study of high density lipoprotein in adult non-insulin dependent diabetics. *American Journal of Epidemiology* 1983;117:186-192.

16. Bauer W, Bennett GA, Zeller JW. The pathology of joint lesions in patients with psoriasis and arthritis. *Transactions of the Association of American Physicians* 1941;56:349-352.

17. Bazin P. *Theoriques et cliniques sur les affections cutaneous de nature arthritique et arthreux*. Paris: Delahaye, 1860.

18. Beaulieu AD, Roy R, Mathon G. Psoriatic arthritis: risk factors for patients with psoriasis- a study based on histocompatibility antigen frequencies. . *Journal of Rheumatology* 1983;10:633-636.

19. Bell JI, Todd JA, McDevitt HO. The molecular basis of HLA disease association. *Advances in Human Genetics* 1989;18:1-41.

20. Benhamou CL, Chamot MA, Khan MF. Synovitis-acne-pustulosis-hyperostosis-osteomyelitis syndrome (SAPHO) - a new syndrome among spondyloarthropathies? *Clinical and Experimental Rheumatology* 1988;6:109-112.

21. Bennett RM. Psoriatic arthritis. In: McCarty DJ, ed. *Arthritis and Allied Conditions*. Philadelphia: Lea and Febiger, 1979. p.642.

22. Bennett RM. Psoriatic arthritis. In: McCarty DJ, ed. *Arthritis and Allied Conditions*. Philadelphia: Lea and Fibiger, 1985. p.850.

23. Berg EL, Yoshino T, Rott LS, et al. The cutaneous lymphocyte antigen is a skin lymphocyte homing receptor to the vascular lectin endothelial cell leukocyte adhesion molecule 1. *Journal of Experimental Medicine* 1991;174:1461-1466.

24. Beutler BA, Cerami A. Recombinant interleukin-1 suppresses lipoprotein lipase activoty in 3T3-L1 cells. *Journal of Immunology* 1985;135:3969-3971.

25. Bevilacqua MP, Nelson RM, Mannori. G, Cecconi O. Endothelial-leukocyte adhesion molecules in human disease. *Annual Review of Medicine* 1994;45:361-378.

26. Blackmore MG, Gladman DD, Husted J, Long JA, Farewell VT. Measuring health status in psoriatic arthritis: The Health Assessment Questionnaire and its modification. *Journal of Rheumatology* 1995;22:886-893.

27. Blumberg BS, Bunin JJ, Calkins E, Pirani CL, Zafler NJ. ARA nomenclature and classification of arthritis and rheumatism (tentative). *Arthritis and Rheumatism* 1964;283:1668-1670.

28. Bourdillon C. *Psoriasis et arthropathies*. Paris: MD Thesis, 1998.

29. Brahn E, Scoville CD. Biochemical markers of disease activity. In: Dixon JS, Bird HA, eds. *Clinical Rheumatology: Biochemical Aspects of Rheumatic Diseases*. London: Bailliere Tindall, 1988. p.153.

30. Brubacher B, Gladman DD, Buskila D, Langevitz P, Farewell VT. Followup in psoriatic arthritis: Relationship to disease characteristics. *Journal of Rheumatology* 1992;19:917-920.

31. Bruckdorfer KR,, Hillary JB, Bunce T, Vancheeswaran R, Black CM. Increased susceptibility to oxidation of low-density lipoproteins isolated from patients with systemic sclerosis. *Arthritis Rheum* 1995;38;8:1060-1067.

32. Brustein DM, Scher RK, Auerbach R. Hyperlipoproteinaemia and psoriasis. *Lancet* 1976;1:154.

33. Buskila D, Langevitz P, Gladman DD, Urowitz S, Smythe HA. Patients with rheumatoid arthritis are more tender than those with psoriatic arthritis. *Journal of Rheumatology* 1992;19:1115-1119.

34. Buyan JP, Yaron M, Lockshin MD. First international conference on rheumatic disease in pregnancy. *Arthritis and Rheumatism* 1993;36:59-64.

35. Camp RDR. Psoriasis. In: Champion RH, Burton JL, Ebling FGH, eds. *Textbook of Dermatology*. Oxford : Blackwell, 1992. p.1359.

36. Campos H, Genest J, Blijlevan SEM,, et al. LDL partical size and coronary artery diseases. *Atherosclerosis and Thrombosis* 1992;12:187-195.

37. Castelli WP, Garrison RJ,, Wilson PWF. Incidence of coronary artery disease and lipoprotein cholesterol levels. *Journal of the American Medical Association* 1986;256:283-285.

38. Cats C. Psoriasis and arthritis. *Cutis* 1990;46:323-329.

39. Clegg DO, Reda DJ, Mejias E, et al. Comparison of sulfasalazine and placebo in the treatment of psoriatic arthritis - A Department of Veterans Affairs cooperative study. *Arthritis and Rheumatism* 1996;39:2013-2020.

40. Coste F, Francon R, Touraine R, Loyou G. Polyarthrite psoriasique. *Revue du Rheumatisme et des Maladies Osteoarticulaires* 1958;25:75-84.

41. Cuellar ML, Marlowe S, Iglesias A, et al. Charcot-like arthropathy: a newly recognised subset of psoriatic arthritis. *Arthritis and Rheumatism* 1996;39;9:S257.(Abstract)

42. Cuéllar ML, Citera G, Espinoza LR. Treatment of psoriatic arthritis. *Bailliere's Clinical Rheumatology* 1994;483-498.

43. Daltroy LH, Larson MG, Roberts WM, Liang MH. A modification of the Health Assessment Quesionnaire for the spondyloarthropathies. *Journal of Rheumatology* 1990;17:946-950.

44. Decker JL. *Psoriatic Arthritis*. Orlando: Grune and Stratton, 1985.

45. Della Valle G, Lubrano E, Di Girolamo C. Prevalenza dell'artrite psoriasica in 746 pazienti con psoriasis osservati nel decennio 1980-1990. In: *Proceedings of the International Symposium 'Artropatia Psoriasica'*. Reggio Emilia, Italy: 1991. p.60.

46. Eastmond CJ. Genetics and HLA antigens. In: Wright V, Helliwell P, eds. *Bailliere's Clinical Rheumatology: Psoriatic Arthritis*. London: Bailliere Tindall, 1994. p.263.

47. Eastmond CJ, Woodrow JC. The HLA system and the arthropathies associated with psoriasis. *Annals of the Rheumatic Diseases* 1977;36:112-120.

48. Eberhardt K, Fex E, Johnson U, Wollhein FA. Associations fo HLA-DRB and -DQB genes with two and five years outcome in rheumatoid arthriits. *Annals of the Rheumatic Diseases* 1996;55:34-39.

49. Espinoza LR. Psoriatic arthriits: further epidemiologic and genetic considerations. In: Gerber LH, Espinoza L R, eds. *Psoriatic arthritis*. Orlando: Grune and Stratton, 1985. p.9.

50. Espinoza LR, Berman A, Vasey FB. Psoriatic Arthritis and Acquired Immunodeficiency Syndromes. *Arthritis and Rheumatism* 1988;21:8:1034-1040.

51. Espinoza LR, Jara LJ, Espinoza CG, Silveira LH, Martinez-Osuna F, Seleznick M. There is an association between human immunodieficiency virus infection and spondyloarthropathies. *Rheumatic Disease Clinics of North America* 1992a;18:257-266.

52. Espinoza LR, Vasey F B, Gaylord SW. Histocompatibility typing in the sero-negative spondyloarthropathies: a survey. *Seminars in Arthritis and Rheumatism* 1982;11:375-381.

53. Espinoza LR, Zakraoui L, Espinoza CG, et al. Psoriatic arthritis: Clinical response and side effects to methotrexate therapy. *Journal of Rheumatology* 1992b;19:872-877.

54. Fairburn K, Kunaver M, WIlkinson LS, Cambridge G, Haskard D, Edwards JCW. Intercellular adhesion molecules in normal synovium. *British Journal of Rheumatology* 1993;32:302-306.

55. Fried SK, Zechner R. TNF decreases human adipose tissue LPL mRNA levels, synthesis and activity. *Journal of Lipid Research* 1989;30(12):1917-1923.

56. Fries JF, Spitz PW, Kraines RG, Holman HR. Measurement of patients outcome in arthritis. *Arthritis and Rheumatism* 1980;23:137-45.

57. Fuchs HA, Pincus T. Radiographic damage in rheumatoid arthritis. Description by nonlinear models. *Journal of Rheumatology* 1992;19:11:1655-1658.

58. Gerber LH, Murray CL, Perlman SG. Human lymphocyte antigens characterising psoriatic arthritis and its subtypes. *Journal of Rheumatology* 1982;9:703-707.

59. Gladman DD. Psoriatic arthritis: recent advances in pathogenesis and treatment. *Rheumatic Disease Clinics of North America* 1992a;18:247-256.

60. Gladman DD. Toward unraveling the mystery of psoriatic arthritis. *Arthritis and Rheumatism* 1993a;36:881-884.

61. Gladman DD. Natural history of psoriatic arthritis. In: Wright V, Helliwell P, eds. *Bailliere's Clinical Rheumatology: Psoriatic Arthritis*. London: Bailliere Tindall, 1994. p.379.

62. Gladman DD, Anhorn KAB, Schachter RK, Mervert H. HLA antigens in psoriatic arthritis. *British Journal of Rheumatology* 1986;13:586.

63. Gladman DD, Brubacher B, Buskila D, Langevitz P, Farewell VT. Psoriatic spondyloarthropathy in men and women: A clinical, radiographic, and HLA study. *Clinical and Investigative Medicine* 1992b;15:371-375.

64. Gladman DD, Brubacher B, Buskila D, Langevitz P, Farewell VT. Differences in the expression of spondyloarthropathy: A comparison between ankylosing spondylitis and psoriatic arthritis. *Clinical and Investigative Medicine* 1993b;16:1-7.

65. Gladman DD, Espinoza LR. International symposium on psoriatic arthritis. *Journal of Rheumatology* 1992c;19:290-291.

66. Gladman DD, Farewell VT. The role of HLA antigens as indicators of disease progression in psoriatic arthritis: Multivariate relative risk model. *Arthritis and Rheumatism* 1995a;38:845-850.

67. Gladman DD, Farewell VT, Nadeau C. Longitudinal study of clinical and radiological progression in psoriatic arthritis. *Journal of Rheumatology* 1990;17(6):809-812.

68. Gladman DD, Farewell VT, Nadeau C. Clinical indicators of progression in psoriatic arthritis: Multivariate relative risk model. *Journal of Rheumatology* 1995b;22:675-679.

69. Gladman DD, Schuckett R, Russell ML. Psoriatic Arthritis (PsA) - An Analysis of 220 Patients. *Quarterly Journal of Medicine* 1987;62; 238:127-141.

70. Gough A, Faint J, Salmon M, Hassell A, Wordsworth P, Pilling D. Genetic typing of patients with inflammatory arthritis at presentation can be used to predict outcome. *Arthritis and Rheumatism* 1994;37:1166-1170.

71. Goupille P, Valat JP. Sulfasalazine in psoriatic arthritis: A new or established indication? *Arthritis and Rheumatism* 1996;39:711-712.

72. Goupille P, Védère V, Roulot B, Brunais J, Valat JP. Incidence of osteoperiostitis of the great toe in psoriatic arthritis. *Journal of Rheumatology* 1996;23:1553-1556.

73. Green J, Montasser M, Low HC, Woodrow JC. Investigation of the association of a number of HLA antigens with psoriasis and psoriatic arthritis. . *Statistics in Medicine* 1988;7:443-450.

74. Gregarson PK. The shared epitope hypothesis. *Arthritis and Rheumatism* 1987;30:1205-1213.

75. Groves RW, Allen MH, Barker JN, Haskard DO, MacDonald DM. Endothelial leucocyte adhesion molecule-1 (ELAM-1) expression in cutaneous inflammation. *British Journal of Dermatology* 1991;124:117.

76. Hanly GS, Russell ML, Gladman DD. Psoriatic spondyloarthropathy - A long-term prospective study. *Annals of the Rheumatic Diseases* 1988;47:386-393.

77. Helliwell P, Marchesoni A, Peters M, Barker M, Wright V. A re-evaluation of the osteoarticular manifestations of psoriasis . *British Journal of Rheumatology* 1991;30:339-345.

79. Helliwell PH, Wright V. Psoriatic arthritis: clinical features. In: Klippel J, Dieppe PAD, eds. *Rheumatology*. 1994.

80. Ilowite NT, Samuel P, Ginzler E, Jacobson MS. Dyslipoproteinaemia in Paediatric SLE. *Arthritis and Rheumatism* 1988;31:859-862.

81. James RW, Marin M, Ruiz J, Pometta D. Factors affecting the low density lipoprotein profile in type II diabetic patients. *Diabetic Medicine* 1994;12:61-65.

82. Jenkinson TR, Armas J, Evison G, Cohen M, Lovell C, McHugh NJ. The cervical spine in psoriatic arthritis: A clinical and radiological study . *British Journal of Rheumatology* 1994;33:255-259.

83. Jones SM, Armas JB, Cohen MG, Lovell CR, Evison G, McHugh NJ. Psoriatic arthritis: Outcome of disease subsets and relationship of joint disease to nail and skin disease . *British Journal of Rheumatology* 1994;33;9:834-839.

84. Jones SM, Dixey J, Hall ND, McHugh NJ. Expression of the cutaneous lymphocyte antigen (CLE) and its counter-receptor E-Selectin in the skin and joints of patients with psoriatic arthritis. *British Journal of Rheumatology* 1997;36;7:748-757.

85. Kammer GM, Soter NA, Gibson DJ, Schur PH. Psoriatic arthritis: A clinical, immunologic and HLA study of 100 patients. *Seminars in Arthritis and Rheumatism* 1979;9:75-97.

86. Kane D, Greaney T, Bresnihan B, Gibney RG, Fitzgeral O. Ustrasound Features of Psoriatic Arthritis. *British Journal of Rheumatology* 1997;36(1):133.(Abstract)

87. Kanter SM, Hsu SH, Bias WB, Arnett FC. Clinical and immunological subsets of psoriatic arthritis. *Clinical and Experimental Rheumatology* 1984;2:105-109.

88. Kay LJ, Walker DJ. Nail and DIP joint involvment in 150 patients with inflammatory arthritis. *British Journal of Rheumatology* 1997;36(1):132.(Abstract)

89. Keat A. HIV and overlap with Reiters syndrome. In: Wright V, Hilliwell P, eds. *Bailliere's Clinical Rheumatology: Psoriatic Arthritis*. London: Bailliere Tindall, 1994. p.363.

90. Kirwan JR. Arthritis and Rheumatism Council Low-Dose Glucocorticoid Study Group. The effect of glucocorticoids on joint destruction in rheumatoid arthritis . *New England Journal of Medicine* 1995;33:142-146.

91. Kirwan JR, Reedback JS. Stanford Health Questionnaire modified to assess disability in British patients with rheumatoid arthritis. *British Journal of Rheumatology* 1986;25:206-209.

92. Laurent MR. Psoriatic arthritis. In: Panayi GS, ed. *Clinics in Rheumatic Diseases*. London: WB Saunders, 1985. p.61.

93. Laurent MR, Panayi GS, Shepherd P. Circulating immune complexes, serum immuoglobulins and acute phase protein in psoriasis and psoriatic arthritis. *Annals of the Rheumatic Diseases* 1981;40:66-69.

94. Lazarevic MB, Vitic J, Mladenovic V, Myones BL, Skosey JL, Swedler WI. Dyslipoproteinemia in the course of active rheumatoid arthritis. *Seminars in Arthritis and Rheumatism* 1992;22:172-180.

95. Leonard DG, O'Duffy JD, Rogers RS. Prospective analysis of psoriatic arthritis in patients hospitalized for psoriasis. *Mayo Clinic Proceedings* 1978;53:511-518.

96. Lindgren FT, Jewson LC, Hatch FT. The isolation and quantitative analyses of serum lipoproteins In. In: Nelson GJ, ed. *Blood lipids and lipoproteins; Quantitation, composition and metabolism.* New York: Wiley Interscience, 1972. p.182.

97. Little H, Harvie JN, Lester RS. Psoriatic arthritis in severe psoriasis. *Canadian Medical Association Journal* 1975;112:317-319.

98. London MG, Muirden KD, Hewitt JV. Serum cholesterol in rheumatic disease. *BMJ* 1963;1:1380-1383.

99. Lorber M, Aviram S, Linn S. Hypocholesterolaemia and abnormal high density lipoprotein in rheumatoid arthritis. *British Journal of Rheumatology* 1985;24:250-255.

100. Maher VMG, Brown BG. Lipoprotein (a) and coronary heart diseases. *Current Opinion in Rheumatology* 1995;6:229-235.

101. Mahrle G, Schulze HJ, Bräutigam M, et al. Anti-inflammatory efficacy of low-dose cyclosporin A in psoriatic arthritis. A prospective multicentre study. *British Journal of Dermatology* 1996;135:752-757.

102. McCormack GD, Barth W. Classification and Diagnosis of Psoriatic Arthritis. In: Gerber LH, Espinoza LR, eds. *Psoriatic Arthritis*. Grune and Stratton, 1985. p.59.

103. McDonagh JE, Dunn A, Ollier WER, Walker DJ. Compound heterozygosity for the shared epitope and the risk and severity of rheumatoid arthritis in extended pedigrees . *British Journal of Rheumatology* 1997;36:322-327.

104. McHugh NJ, Laurent MR. The effect of pregnancy on the onset of psoriatic arthritis. *British Journal of Rheumatology* 1989;28:50-52.

105. McHugh NJ, Laurent MR, Treadwell BLJ, Tweed JM, Dagger J. Psoriatic arthritis: clinical subgroups and histocompatibility antigens. *Annals of the Rheumatic Diseases* 1987;46:186-188.

106. McKendry RJR, Senger DPS, DesGroseilliers JP, Dunne JV. Frequency of HLA antigens in patients with psoriasis of psoriatic arthritis. *Canadian Medical Association Journal* 1984;130:411-415.

107. Molin J. Psoriatic arthritis. *Annals of Clinical Research* 1978;8:305-311.

108. Moll JMH. The clinical spectrum of psoriatic arthritis. *Clinical orthopaedics and Related Research* 1979;143:66-75.

109. Moll JMH. Psoriatic arthritis (editorial). *British Journal of Rheumatology* 1984;23:241-245.

110. Moll JMH. The place of psoriatic arthritis in the spondarthritides. *Bailliere's Clinical Rheumatology* 1994;395-417.

111. Moll JMH, Haslock I, Macrae IF, Wright V. Association between ankylosing spondylitis, psoriatic arthritis, Reiters disease, the intestinal arthropathies and Behcets syndrome. *Medicine (Baltimore)* 1974;54:343-364.

112. Moll JMH, Wright V. Psoriatic arthritis. *Seminars in Arthritis and Rheumatism* 1973;3:55-78.

113. Nigon F, Resnik P, Rouis M, Chapman MJ. Discrete subspecies of human low density lipoprotein are heterogeneous in their interaction with the cellular LDL receptor. *Journal of Lipid Research* 1998;1992:1749-1753.

114. Nissila M, Isomake H, Kaarela K. Prognosis of inflammatory joint diseases. A three year follow-up study. *Scandinavian Journal of Rheumatology* 1983;12:33-38.

115. O'Neill T, Evison G, Bhalla AK. Pseudoarthroplastic' hand in arthritis mutilans. *British Journal of Rheumatology* 1992;31:559-560.

116. Ogawa H, Nielson S, Kawakami M. TNF and IL-1 show different modes of combined effect on LP activiey and intracellular lipolysis in 3T2-L1 cells. *Biochem Biophys Acta* 1998;1003(2):131-135.

117. Olerup O, Aldener A, Fogdell A. HLA-DQB1 and -DQA1 typing by PCR amplification with sequence-specific primers (PCR-SSP) in 2 hours. *Tissue Antigens* 1993;41:119-134.

118. Olerup O, Zetterquist H. HLA-DRB1*01 subtyping by allele-specific PCR amplification: A sensitive, specific and rapid technique. *Tissue Antigens* 1991;37:197-204.

119. Olerup O, Zetterquist H. HLA-DR typing by PCR amplification with sequence-specific primers (PCR-SSP) in 2 hours: An alternative to serological DR typing in clinical practice including donor-recipient matching in cadaveric transplantation. *Tissue Antigens* 1992;39:225-235.

120. Olerup O, Zetterquist H. DR "low-resolution" PCR-SSP typing - a correction and an up-date. *Tissue Antigens* 1994;55-56.

121. Olivieri I, Barozzi L, Pierro A, De Matteis M, Padula A, Pavlica P. Toe dactylitis in patients with spondyloarthropathy. Assessment by magnetic resonance imaging. *Journal of Rheumatology* 1997;24;5:926-930.

122. Oriente P, Biondi-Oriente C, Scarpa R. Clinical manifestations. In: Wright V, Helliwell P, eds. *Bailliere's Clinical Rheumatology: Psoriatic Arthritis*. Bailliere Tindall, 1994. p.277.

123. Ostensen M. The effect of pregnancy on ankylosing spondylitis, psoriatic arthritis and juvenile arthritis. *American Journal of Reproductive Immunology* 1992;28:235-237.

124. Ostensen M, Husby G. A prospective clinical study of the effect of pregnancy on rheumatoid arthritis and ankylosing spondylitis. *Arthritis and Rheumatism* 1983;26:1155-1159.

125. Ostensen M, Lee Nelson J. Bits and pieces in a puzzle- rheumatoid arthritis and pregnancy. *British Journal of Rheumatology* 1995;34:1-7.

126. Panayi. GS. Immunology of psoriasis and psoriatic arthritis. In: Wright V, Helliwell PS, eds. *Bailliere's Clinical Rheumatology*. Bailliere, 1994. p.419.

127. Picker LJ, Kishimoto K, Smith CW, Warnock RA, Butcher EC. ELAM-1 is an adhesion molecule for skin-homing T-cells . *Nature* 1991;349:796-799.

128. Picker LJ, Michie LS, Rott LS, Butcher EC. A unique phenotype of skin-associated lymphocytes in humans: preferential expression o fthe HECA-452 epitope by benign and malignant T-cells at cutaneous sties. *American Journal of Pathology* 1990;136:1053.

129. Picker LJ, Treer J.R. , Ferguson-Darnell B, Collins PA, Bergstrsser R, Terstappen LWMM. Control of Lymphocyte Recirculation in Man II. Differential Regulation of the Cutaneous Lymphocyte -Associated Antigen, a Tissue-Selective Homing Receptor for Skin-Homing T Cells. *Journal of Immunology* 1993;1122-1136.

130. Pincus T. Long-term outcomes in rheumatoid arthritis. *British Journal of Rheumatology* 1995;34 (Suppl):59-73.

131. Pitzalis C, Cauli A, Pipitone N, et al. Cutaneous lymphocyte antigen-positive T lymphocytes preferentially migrate to the skin but not to the joint in psoriatic arthritis. *Arthritis and Rheumatism* 1996;39:137-145.

132. Potter EM, McEwan C. Psoriatic Arthritis: clinical features with particular reference to distal interphalangeal joint involvement. *British Journal of Rheumatology* 1992;31:646-647.

133. Rantapaa-Dahlqvist S, Walberg-Jonsson S, Dahlen G. Lipoprotein (a), lipids, and lipoproteins in patients with rheumatoid arthritis. *Annals of the Rheumatic Diseases* 1991;50:366-368.

134. Regnstron J, Nilsson J, Tornwall P, Landdou C, Hamstn A. Susceptibility to low density lipoprotein oxidation and coronary atherosclerosis in man. *Lancet* 1992;12:187-195.

135. Ritchie DM, Boyle JA, McInnes JM. Clinical studies with an articular index of the assessment of joint tenderness in patients with rheumatoid arthritis. *Quarterly Journal of Medicine* 1968;37:393-406.

136. Roberts MET, Wright V, Hill AGS, Mehra AC. Psoriatic arthritis: follow-up study. *Annals of the Rheumatic Diseases* 1976;35:206-212.

137. Rogers J, Watt I, Dieppe P. Arthritis in Saxon and mediaeval skeletons. *BMJ* 1981;283:1668-1670.

138. Rosengren A. Lipoprotein(a) and coronary artery disease: a prospective case-controlled study in a general population sample of midle-aged men. *BMJ* 1990;301:1248-1251.

139. Rosenzweig IB, Wiebe DA,, Borden EC. Plasma lipoprotein changes in humans induced by beta interferon. *Atherosclerosis* 1987;647:261-267.

140. Rossner S, Lofmark C. Dyslipoproteinaemia in patients with active, chronic polyarthritis. A study on serum lipoproteins and triglyceride clearance (intravenous fat tolerance test). *Atherosclerosis* 1977;28:41-52.

141. Rowe IF, Soutar AK, Trayner IM. Circulating human C-reactive protein binds very low-density lipoproteins. *Clinical and Experimental Immunology* 1984;53:237-244.

142. Salvarani C, Cantina F, Olivieri I, Portoli I. Isolated peripheral enthesitis and/or dactylitis: A subset of psoriatic arthritis. *Journal of Rheumatology* 1997;22: 6:1106-1110.

143. Salvarani C, Macchioni P, Boiardi L, et al. Low dose cyclosporine A in psoriatic arthritis: Relation between soluble interleukin 2 receptors and response to therapy. *Journal of Rheumatology* 1992;19:74-79.

144. Salvarani C, Macchioni PL, Zizzi F. Clinical subgroups and HLA antigens in Italian patients with psoriatic arthrits. *Clinical and Experimental Rheumatology* 1989;7:391-396.

145. Scarpa R, Biondi Oriente C, Oriente P. The classification of psoriatic arthritis: what will happen in the future? *Journal of the American Academy of Dermatology* 1997;36(1):78-83.

146. Scarpa R, Del Puente A, Di Girolamo C, Della Valle G, Lubrano E, Oriente P. Interplay between environmental factors, articular involvement, and HLA-B27 in patients with psoriatic arthritis. *Annals of the Rheumatic Diseases* 1992a;51:78-79.

147. Scarpa R, Della Valle G, Lubrano E, Di Girolamo C, Del Puente A, Oriente P. Psoriatic arthritis (PA): a harmless disease? *British Journal of Rheumatology* 1992b;31:209-214.

148. Scarpa R, Oriente P, Pulima A. Psoriatic arthritis in psoriatic patients. *British Journal of Rheumatology* 1984;23:246-250.

149. Scott DL, Coulton BL, Popert AJ. The long-term progression of joint damage in rheumatoid arthritis. *Annals of the Rheumatic Diseases* 1986;45:373-378.

150. Scott DL, Symmons DPM, Coulton BL. The longtern outcome of treating rheumatoid arthritis: results after 20 years. *Lancet* 1987;i:1108-1111.

151. Seishima M, Mori S, Noma A. Serum lipid and apolipoprotein levels in paitents with psoriasis. *British Journal of Dermatology* 1994;130:737-742.

152. Sharp JT, Lidsky MD, Collins LC. Methods of scoring the progression of radiological changes in RA. *Arthritis and Rheumatism* 1971;14: 6:706-720.

153. Sharp JT, Young YD, Bum GB,. How many joint in the hands and wrists should be included in the score of radiological abnormalities used to assess RA . *Arthritis and Rheumatism* 1985;28:1326-1335.

154. Sherman MS. Psoriatic arthritis: observations on the clinical, roentgenographic and pathological changes. *Journal of Bone and Joint Surgery* 1952;34A:831-852.

155. Silman A, Kay A, Brenan P. Timing of pregnancy in relation to the onset of rheumatoid arthritis. *Arthritis and Rheumatism* 1992;35:152-155.

156. Sitton NG, Dixon JS, Bird HA, Wright V. Serum biochemistry in rheumatoid arthritis, seronegative arthropathies, osteoarthritis, SLE and normal subjects. *British Journal of Rheumatology* 1987;26:131-135.

157. Spriggs DR, Sherman ML, Mitchie H. Recombinant human TNF adminstered as a 24-hour infusion. *Journal of the National Cancer Institute* 1988;80:1039-1044.

158. Stastny P, Ball EJ, Dry PJ, Nurez G. The human immune response region (HLA-D) and disease susceptibility. *Immunological Reviews* 1983;70:115-154.

159. Stockman A, Emery P, Doyle T, Hopper J, Tait B, Muirden K. Relationship of progression of radiographic changes in hands and wrists, clinical features and HLA-DR antigens in rheumatoid arthritis. *Journal of Rheumatology* 1991;18:1001-1007.

160. Svenson KLG, Lithell H, Hallgren R, Selinus I, Vessby B. Serum lipoprotein in active rheumatoid arthritis and other chronic inflamatory arthritides. *Archives of Internal Medicine* 1987;147:1912-1916.

161. Terres W, Tatsis E, Pfalzer B,, Beil U, Beisiegel U, Hamm CW. Rapid angiographic progression of coronary heart disease in patients with elevated lipoprotein (a). *Circulation* 1995;91:948-950.

162. Thomson W, Pepper L, Payton A, Carthy A, Scott D, Ollier W. Absence of an assocation between HLA-DRB1*04 and rheumatoid arthritis in newly diagnossed cases from the community. *Annals of the Rheumatic Diseases* 1993;52:539-541.

163. Tiwari JL, Terasake PI. *HLA and Disease Associations*. New York: Springer-Verlag, 1985.

164. Torre Alonso JC, Rodriguez Perez A, Arribas Castrillo JM. Psoriatic Arthritis (PA): A clinical, immunological and radiological study of 180 patients. *British Journal of Rheumatology* 1991;31:245-50.

165. Van Romunde LKJ, Cats A, Hermans J, Valkenberg HA, de Vries E. Psoriasis and arthritis. III: a cross-sectional comparative study of patients with psoriatic arthritis and sero-negative and sero-positive polyarthritis: radiological and HLA aspects . *Rheumatology International* 1984a;4:67-73.

166. Van Romunde LKJ, Cats A, Hermans J, Valkenburg HA. Psoriasis and arthritis II. A cross-sectional study of patients with 'psoriatic arthritis' and seronegative and seropositive polyarthritis: clinical aspects. *Rheumatology International* 1984b;4:61-65.

167. Van Romunde LKJ, Valkenberg HA, Swart-Bruinsma W, Cats A, Hermans J. Psoriasis and arthritis. I: A population study. *Rheumatology International* 1984c;4:55-60.

168. van Zeben D, Hazes JMW, Zwinderman AH, Cats A, Schreuder GMT, D'Amaro J. Associaiton of HLA-DR4 with a more progressive disease course in patients with rheumatoid arthritis. *Arthritis and Rheumatism* 1991;34:822-830.

169. Veale D and Fitzgerald, O. Psoriatic arthritis-'DIP' or not DIP?' that is the question. *British Journal of Rheumatology* 1992;31:430

170. Veale D, Rogers S, Fitzgerald O. Classification of clinical subsets in psoriatic arthritis. *British Journal of Rheumatology* 1994;33:133-138.

171. Veale D, Rogers S, Fitzgerald O. Immunolocalization of adhesion molecules in psoriatic arthritis, psoriatic and normal skin. *British Journal of Rheumatology* 1995;132:32-38.

172. Veale D, Yanni G, Rogers S, Barnes L, Bresnihan B, Fitzgerald O. Reduced synovial membrane macrophage numbers, ELAM-1 expression, and lining layer hyperplasia in psoriatic arthritis as compared with rheumatoid arthritis. *Arthritis and Rheumatism* 1993;36:893-900.

173. Vilanova X, Pinol J. Psoriasis arthropathica. *Rheumatism* 1951;7:197-208.

174. Wagner SA, Peter RU, Adam O, Ruzicka T. Therapeutic efficacy of oral low-dose cyclosporin A in severe psoriatic arthritis. *Dermatology* 1993;186:62-67.

175. Walton K, Dyer PA, Grennan DM, Haemey M, Harris R. Clinical features and HLA-DR antigens in rheumatoid arthritis. *Journal of Rheumatology* 1985;12:223-226.

176. Wassenberg S, Rau R. Problems in evaluating radiographic findings in RA using different methods of radiographic scoring: Examples of difficult cases and a study design to develop an improved scoring method. *Journal of Rheumatology* 1995;22:1990-1996.

177. Winyard PG, Tatzbar F, Esterbauer H, Kus ML, Blake DR, Morris CJ. Presence of foam cells containing oxidised low density lipoprotein in the synovial membrane from patients with rheumatoid arthritis . *Annals of the Rheumatic Diseases* 1993;52:677-680.

178. Wolfe F, Cathey MA. The assessment and prediction of funtional disability in rheumatoid arthritis. *Journal of Rheumatology* 1991;18:1298-1306.

179. Wolfe F, Hawley DJ, Cathey MA. Clinical and health status measures over time: prognosis and outcome assessment in rheumatoid arthritis. *Journal of Rheumatology* 1991;18:1290-1297.

180. Wong D, Gladman DD, Husted J, Long J, Farewell V. Mortality studies in psoriatic arthritis. *Arthritis and Rheumatism* 1997;10:1867-1972.

181. Wright V. Psoriasis and Arthritis. *Annals of the Rheumatic Diseases* 1956;15:348-356.

182. Wright V. Rheumatism and psoriasis: a re-evaluation. *American Journal of Medicine* 1959a;27:454-462.

183. Wright V. Psoriatic arthritis - a comparative study of rheumatoid arthritis and arthritis associated with psoraisis. *Archives of Dermatology* 1959b;80:27-35.

184. Wright V. Psoriatic arthritis. *American Journal of Medicine* 1959c;27:123-131.

185. Wright V. Psoriatic arthritis: a comparative study of rheumatoid arthritis and arthritis associated with psoriasis. *Annals of the Rheumatic Diseases* 1961;20:123-131.

186. Wright V. Psoriatic Arthritis. *ARC Reports on Rheumatic Diseases (Series 2) Topical Reviews* 1992;21:

187. Wright V, Moll JMH. Psoriatic arthritis. *Bulletin of the Rheumatic Diseases* 1971;21:627-632.

188. Wright V, Moll JMH. *Psoriatic Arthritis*. Amsterdam: North Holland Publishing, 1976.

189. Young A, Jaraquemada D, Awad J, Festenstein H, Corbett M, Hay FC. Association of HLA-DR4/Dw4 and DR2.Dw2 with radiologic kchanges in a prospective study of patients with rheumatoid arthritis. *Arthritis and Rheumatism* 1984;27:20-25.

190. Zetterquist H, Olerup O. Identification of the HLA-DRB1*04, -DRB1*07, and -DRB1*09 alleles by PCR amplification with sequence-specific primers (PCR-SSP) in 2 hours. *Human Immunol* 1992;34:64-74.

191. Zias J, Mitchell P. Psoriatic arthritis in a fifth-century Judean desert monastery. *Am J Phys Anthropol* 1996;101:491-502.

# APPENDICES

## APPENDIX A

**Derivation of PASI Score**

This is a commonly used scoring system to combine the extent and severity of skin lesions (Camp, 1992)

| Extent (%) | Score | Severity | Score |
|---|---|---|---|
| <10 | 1 | Nil | 0 |
| 10-29 | 2 | Slight | 1 |
| 30-49 | 3 | Moderate | 2 |
| 50-69 | 4 | Severe | 3 |
| 70-89 | 5 | Very severe | 4 |
| 90-100 | 6 | | |

| | Extent | Severity | | | |
|---|---|---|---|---|---|
| | | Erythema | Infiltration | Desquamation | PASI |
| Head | A | B | C | D | 0.1(B+C+D)A |
| Arms | A | B | C | D | 0.2(B+C+D)A |
| Trunk | A | B | C | D | 0.3(B+C+D)A |
| Legs | A | B | C | D | 0.4(B+C+D)A |
| Total | | | | | 0-72 |

**Derivation of Nail Score**

Devised for this study. Hands scored only

Score = Number of nails with pits +

Number of nails with onycholysis +

Number of nails with hyperkeratosis or salmon patches +

Number of nails with "dystrophy"*

Total = 0 - 40

*"Dystrophy" - defined here severe nail deformity involving both sides of the nail.

The score was recorded as follows:-

| | Right | | | | | Left | | | |
|---|---|---|---|---|---|---|---|---|---|
| | L | R | M | I | T | T | I | M | R |
| L | | | | | | | | | |
| Pitting | | | | | | | | | |
| Onych | | | | | | | | | |
| Hyperker | | | | | | | | | |
| Salmon | | | | | | | | | |
| Dystrophy | | | | | | | | | |

Nail Score =

# APPENDIX B

# DEVELOPMENT AND VALIDATION OF A MODIFIED SHARP'S INDEX FOR THE HANDS IN PSORIATIC ARTHRITIS

Radiographic erosions have been used as an important outcome measure in rheumatoid arthritis, particularly in the assessment of therapeutic agents (Kirwan 1995). In rheumatoid arthritis, radiographic hand and wrist damage is thought to mirror the overall progression of damage at other joints (Scott et al 1986) and there is abundant literature regarding the pattern of damage, progression of damage and scoring methods (Fuchs and Pincus 1992; Wassenberg and Rau 1995). In early rheumatoid arthritis, 70% of patients have radiological change at three years; at ten years radiographic progression is invariable and by twenty years most patients have extensive progression despite therapy (Scott et al 1987). Few studies have examined this in psoriatic arthritis.

Studies evaluating hand radiographs in psoriatic arthritis have used various systems devised for rheumatoid arthritis. The ARA radiological scoring system has been used (Torre Alonso et al 1991 and Gladman et al 1987) as has the New York criteria (Veale et al 1994). In the prospective follow-up study presented in Chapter 2b, a modified version of Sharp's 1971 scoring system has been used (Sharp et al 1971). The system has been validated in rheumatoid arthritis, includes the distal interphalangeal joints and is one of the most sensitive scoring systems to detect progressive changes (Sharp et al 1985, Pincus et al 1995). A detailed description of the index, its modification for psoriatic arthritis and validity is described below and should be read in conjunction with Chapter 2b.

**Construct, Face and Content Validity**

A radiological scoring system for the hands was required to score for the DIP joints and wrists as well as the PIP and MCP joints, with sub-divisions for severity of erosions and joint space narrowing, and a score for ankylosis. Sharp's original scoring system (1971) was therefore selected as being the only system that met these criteria (Sharp et al 1971). It has been well validated in rheumatoid arthritis.

***Quantitative differences***

The modified Sharp's index was used to calculate joint space abnormality (JSA) and erosion (ERO) scores and to determine the rates of their progression.

*Joint space abnormality*

In psoriatic arthritis joint space widening due to osteolysis can occur even after apparent radiographic ankylosis (pseudoankylosis) (Balakrishnan, Jones et al, 1996 (see Appendix E)), a phenomenon observed in three patients. Furthermore ankylosis and gross jont widening due to osteolysis can occur at different joints in the same patient (Gladman et al 1993b). These factors make both ankylosis and gross widening probable end points of radiological progression in psoriatic arthritis. Hence Sharp's joint space narrowing (JSN) score was modified, so both these extreme lesions were given maximum scores. The JSN score was renamed joint space abnormality (JSA) and was calculated as follows:-

1-focal, 2-<50% reduction, 3 - >50% reduction and 4 -ankylosed or widened.

Joints analysed: 14 finger joints, 5 CMC joints, trapezium-navicular, navicular-lunate, lunate triquetrum, triquetrum-hamate, hamate-capitate, capitate-navicular-lunate, radiocarpals and radioulnar joints. A total of 27 joints areas were assessed with a maximum score of 216 per patient.

The JSA index and the rate of progression was calculated as follows:-

$$\text{Corrected joint space abnormality score (JSAc)} = \frac{\text{total JSA per film}}{\text{216 (maximum score)}} \times 5$$

$$\text{Rate of progression of JSA} = \frac{\text{JSAc}}{\text{Time in months from onset of psoriatic arthritis (T1)}}$$

$$\text{Rate of progression of JSA (baseline to follow up)} = \frac{\text{JSAc}}{\text{Time in months between baseline and follow up (T2)}}$$

*Erosion*

The severity of erosions was determined on a 5 point scale: 1 point for each erosion up to 4, and for erosions over and above 5 a score of 5 was allotted. The size fo the erosion was also taken into consideration to some extent and large denudations (>50% fo articular surface area) of articular surface were designated 5 points.

Joints analysed: 14 finger joints, 5 metacarpal bases, 6 carpal bones, lower end radius and lower end ulna. A total of 27 joints areas were assessed with a maximum score of 270 per patient.

The ratios used for analysis were calculated as follows:-

$$\text{Corrrected erosion score (defect score, Dc)} = \frac{\text{total number of erosions per film}}{\text{270 (maximum score)}} \times 4$$

$$\text{Rate of progression} = \frac{\text{Dc}}{\text{T1}}$$

Rate of progression from baseline to follow up =

$$\frac{\text{Dc}}{\text{T2}}$$

*Qualitative differences*

Evaluation of the radiographs also allowed documentation of the pattern of involvement and other radiological features of interest which have been reported as being characteristic of psoriatic arthritis. The following signs have been reported as differentiating PsA from RA:- phalangeal tufts, osteolysis, bony proliferation, periostitis, asymmetry, apparent joint space widening and bony ankylosis. Juxta-articular osteopaenia, soft tissue swelling, DIP and wrist involvement were also noted and malalignment was graded as moderate (subluxation) or severe (dislocation).

The cumulative scores for erosions and joint space abnormalities at baseline and at follow-up increased for all joints except for the joint space abnormality score for the proximal interphalangeal joint of the right hand (see Table 5, Chapter 2b). This may reflect the inclusion of joint space widening in the joint space abnormality score. For example, one patient with mutilating disease had radiographic ankylosis (score 4) followed by a reappearance of the joint space (score 0), although the latter

represented an extension of the pathological process and should possibly have been scored as 4 for joint space widening. In this case the length of the phalanx should me measured and the contours of the joint carefully assessed so that the appropriate score is given.

In the process of scoring, comprehensive information regarding other features could be obtained. The progression of these features is detailed fully in Chapter 2b.

**Criterion Validity**

This requires significant correlations with gold standard or other accepted measures. There are no gold standards for the evaluation of hand radiographs in psoriatic arthritis. However, other outcome measures including total clinical joint damage scores and hand and wrist joint damage scores and the rates or their progression were correlated with Sharp's erosion and joint space abnormality scores.

**Discriminant Validity (Responsiveness)**

This represents the capacity of an instrument to measure difference of change. The modified Sharp's index is sensitive to change in a singe joint in the hand or wrist.

**Reliability and Inter-observer variability**

The radiographs in the study presented in Chapter 2b were scored by a single observer (CB) after training and reaching agreement with a radiologist (GE). Reliability was good. Fifteen radiographs were scored blindly by a second observer to assess inter-observer variability (SJ). Without training the differences were large; however the differences reduced after training. I recommend that in any large study of psoriatic arthritis using multiple scorers, the index is extensively piloted and tested first to reduce inter-observer variability.

**Conclusion**

The selection of the index and its modification was deemed sensible in terms of clinical knowledge, satisfying the requirements for credibility and relevance. It correlated with other measures of joint progression in psoriatic arthritis and was a sensitive measure of change. Reliability is good when a single observer is used to score all radiographs, but the complexity and detail of the index requires a comittment to training when multiple observers are used.

# APPENDIX C

## Modified Richie and Joint Swelling Scores

The modified Richie scores (70 joints) and joint swelling scores (66 joints) were recorded as follows:-

| Right | | Joint | Left | |
|---|---|---|---|---|
| **Pain/Tenderness** | **Swelling** | | **Pain/Tenderness** | **Swelling** |
| | | Temporo-mandibular | | |
| | | Sterno-clavicular | | |
| | | Acromio-clavicular | | |
| | | Shoulder | | |
| | | Elbow | | |
| | | Wrist | | |
| | | MCP 1 | | |
| | | MCP 2 | | |
| | | MCP 3 | | |
| | | MCP 4 | | |
| | | MCP 5 | | |
| | | IP (thumb) | | |
| | | PIP 2 | | |
| | | PIP 3 | | |
| | | PIP 4 | | |
| | | PIP 5 | | |
| | | DIP 2 | | |
| | | DIP 3 | | |
| | | DIP 4 | | |
| | | DIP | | |
| | X | Hip | | X |
| | | Knee | | |
| | | Ankle | | |
| | | Talocalcaneal | | |
| | | Midtarsal | | |
| | | MTP 1 | | |
| | | MTP 2 | | |
| | | MTP 3 | | |
| | | MTP 4 | | |
| | | MTP 5 | | |
| | | IP 1 | | |
| | | Toe 2 | | |
| | | Toe 3 | | |
| | | Toe 4 | | |
| | | Toe 5 | | |

**Axial Disease** was noted but not scored.

**Swelling** was either present (score 1) or absent (score 0).

**Pain/tenderness** was scored as follows: 0 = None; 1 = Minimal (positive response on questioning); 2 = Moderate (spontaneous response elicited); 3 = Severe (withdrawal by patient on examination)

## Disease Activity Score (DAS) Modified for Psoriatic Arthritis

A disease activity score combining three variables has been validated in rheumatoid arthritis (Assessing Joint Activity in Rheumatoid Arthritis, Eular 1993). No combined score has been validated for use in psoriatic arthritis, so the Eular score was assessed for use, and subsequently employed, in the study of Chapter 2c. The four variable disease activity score, using the patient's global assessment as the fourth variable, was clearly inappropriate because this may also reflect skin activity.

In rheumatoid arthritis, a change of 1.08 represents a significant improvement or deterioration. Because psoriatic arthritis causes less pain and tenderness than rheumatoid arthritis, fewer joints are involved, and the acute phase response is less pronounced, a smaller difference between scores would be expected to represent a significant change. A single observer, the author, performed all the Ritchie and joint swelling metrology after intensive training and practice in the clinic and the intra-observer variation was low. Hence, for the purpose of this study, any increase in the score was deemed to represent a deterioration in disease activity, and any decrease an improvement.

The disease activity score was calculated as follows:-

Three variables:

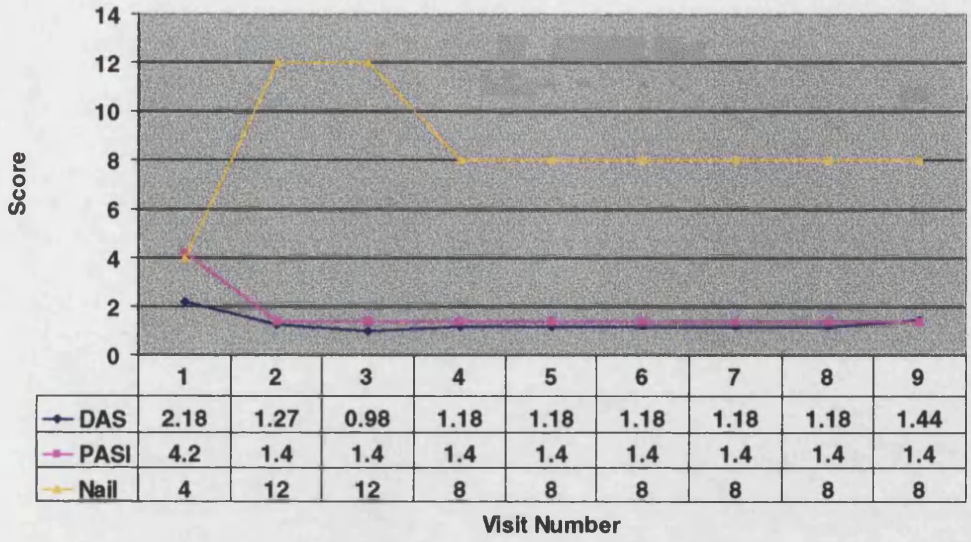
DAS = 0.54* (square root (Modified Richie index))
+ 0.065 (swollen joint count)
+ 0.33*ln (ESR)+0.224

# APPENDIX D

## Temporal Relationship Data (Chapter 2c)

The following graphs show the relationship between joint disease activity scores (DAS), skin scores (PASI) and nail scores at each of the nine time-points for the 24 patients.

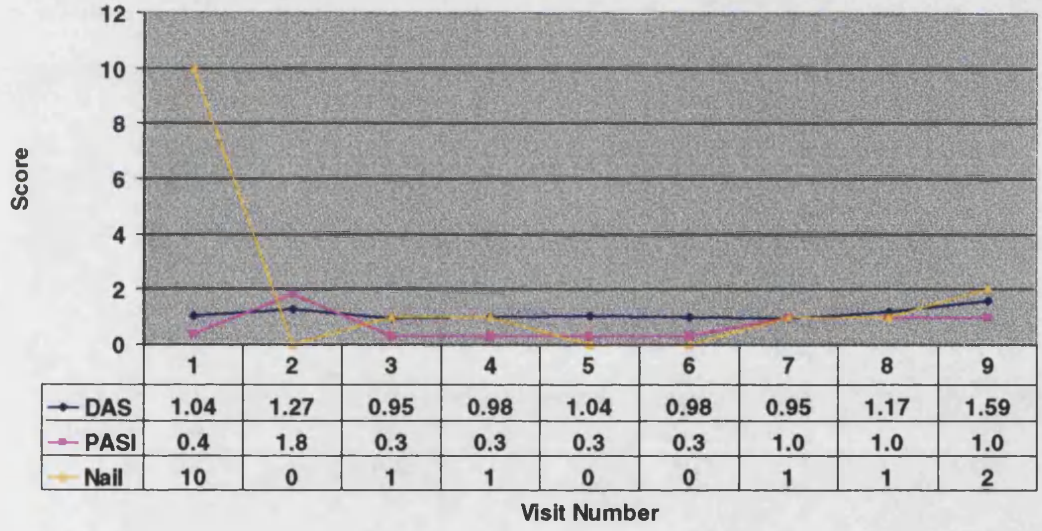
## Patient 1




| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|
| DAS | 2.18 | 1.27 | 0.98 | 1.18 | 1.18 | 1.18 | 1.18 | 1.18 | 1.44 |
| PASI | 4.2 | 1.4 | 1.4 | 1.4 | 1.4 | 1.4 | 1.4 | 1.4 | 1.4 |
| Nail | 4 | 12 | 12 | 8 | 8 | 8 | 8 | 8 | 8 |

Visit Number

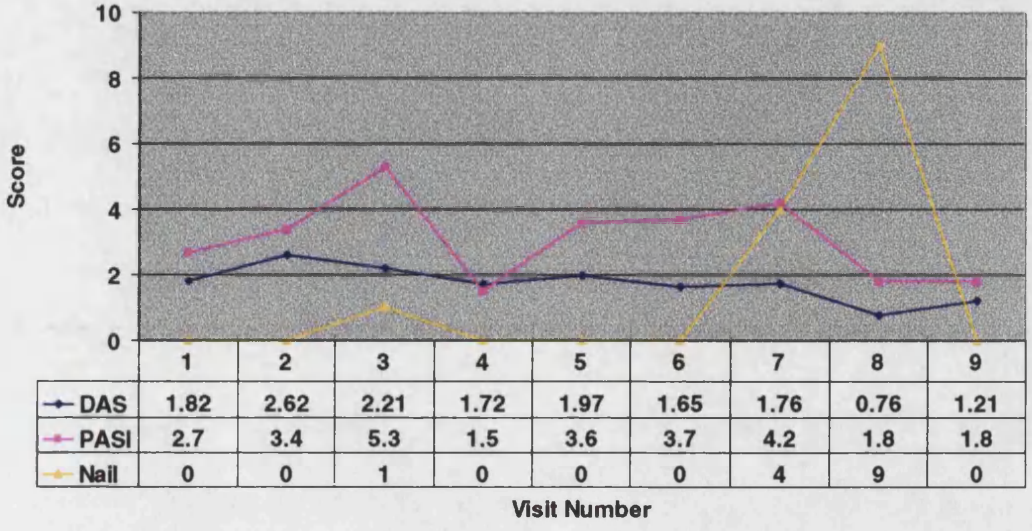
## Patient 2




| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|
| DAS | 1.04 | 1.27 | 0.95 | 0.98 | 1.04 | 0.98 | 0.95 | 1.17 | 1.59 |
| PASI | 0.4 | 1.8 | 0.3 | 0.3 | 0.3 | 0.3 | 1.0 | 1.0 | 1.0 |
| Nail | 10 | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 2 |

Visit Number

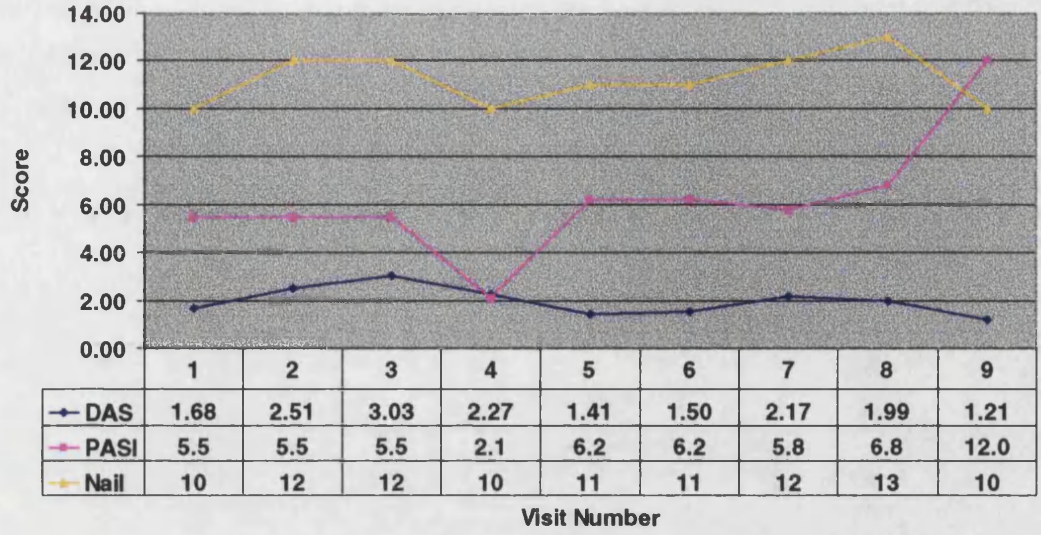
## Patient 3




| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|
| DAS | 1.82 | 2.62 | 2.21 | 1.72 | 1.97 | 1.65 | 1.76 | 0.76 | 1.21 |
| PASI | 2.7 | 3.4 | 5.3 | 1.5 | 3.6 | 3.7 | 4.2 | 1.8 | 1.8 |
| Nail | 0 | 0 | 1 | 0 | 0 | 0 | 4 | 9 | 0 |

Visit Number

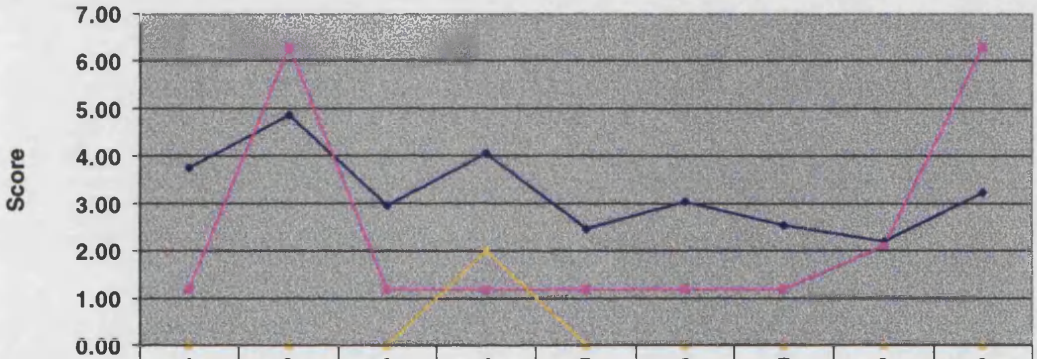
## Patient 4




| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|
| DAS | 1.68 | 2.51 | 3.03 | 2.27 | 1.41 | 1.50 | 2.17 | 1.99 | 1.21 |
| PASI | 5.5 | 5.5 | 5.5 | 2.1 | 6.2 | 6.2 | 5.8 | 6.8 | 12.0 |
| Nail | 10 | 12 | 12 | 10 | 11 | 11 | 12 | 13 | 10 |

Visit Number

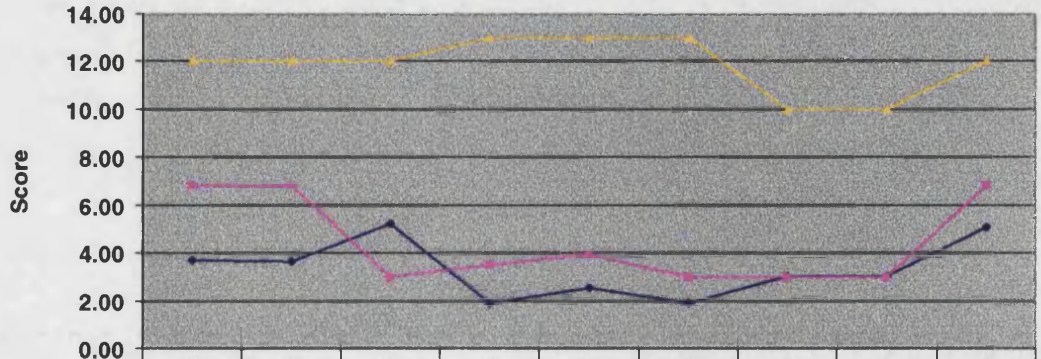
## Patient 5




| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|
| DAS | 3.76 | 4.86 | 2.95 | 4.06 | 2.47 | 3.04 | 2.53 | 2.19 | 3.23 |
| PASI | 1.2 | 6.3 | 1.2 | 1.2 | 1.2 | 1.2 | 1.2 | 2.1 | 6.3 |
| Nail | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |

Visit Number

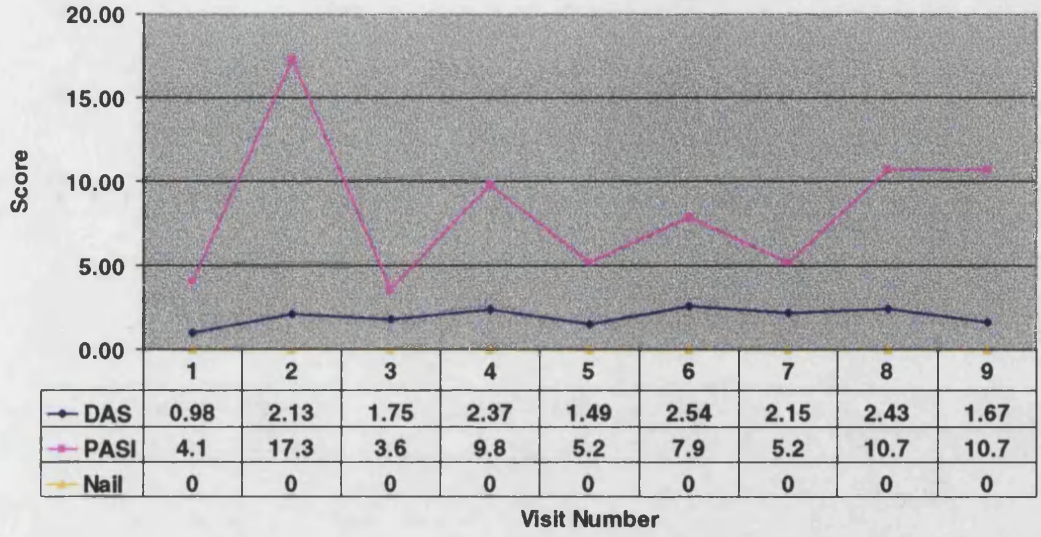
## Patient 6




| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|
| DAS | 3.68 | 3.66 | 5.20 | 1.87 | 2.52 | 1.87 | 3.05 | 3.05 | 5.05 |
| PASI | 6.8 | 6.8 | 3.0 | 3.5 | 3.9 | 3.0 | 3.0 | 3.0 | 6.8 |
| Nail | 12 | 12 | 12 | 13 | 13 | 13 | 10 | 10 | 12 |

Visit Number

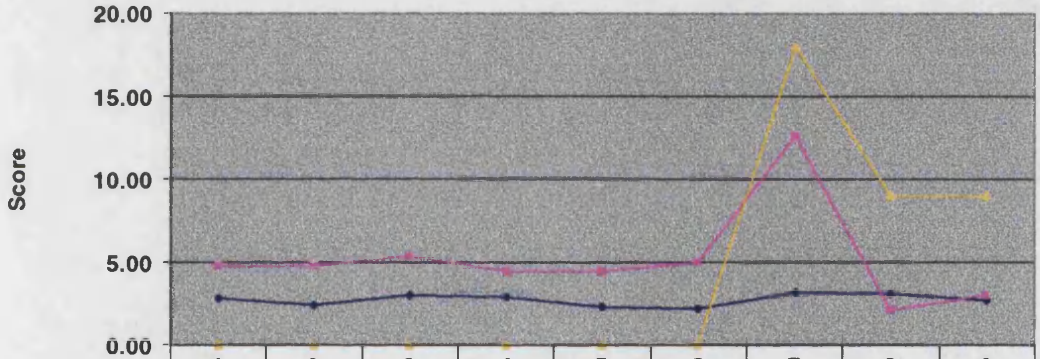
## Patient 7




| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|
| DAS | 0.98 | 2.13 | 1.75 | 2.37 | 1.49 | 2.54 | 2.15 | 2.43 | 1.67 |
| PASI | 4.1 | 17.3 | 3.6 | 9.8 | 5.2 | 7.9 | 5.2 | 10.7 | 10.7 |
| Nail | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

Visit Number

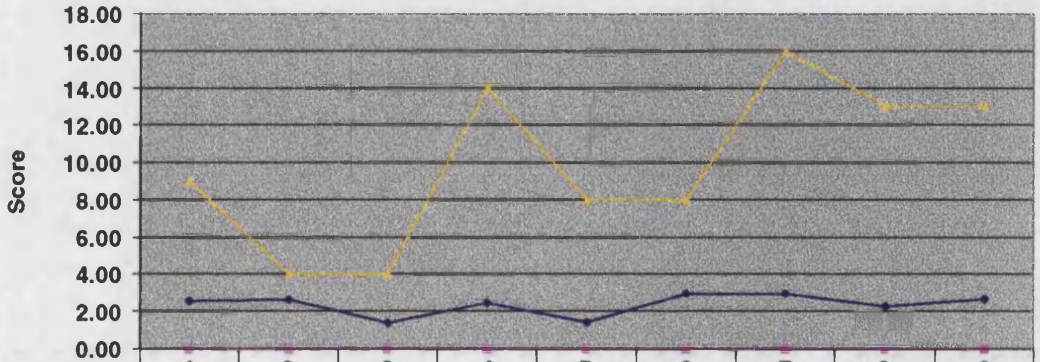
## Patient 8




| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|
| Series1 | 2.80 | 2.45 | 2.99 | 2.87 | 2.30 | 2.19 | 3.19 | 3.12 | 2.68 |
| Series2 | 4.8 | 4.8 | 5.4 | 4.5 | 4.5 | 5.0 | 12.6 | 2.1 | 3.0 |
| Series3 | 0 | 0 | 0 | 0 | 0 | 0 | 18 | 9 | 9 |

Visit Number

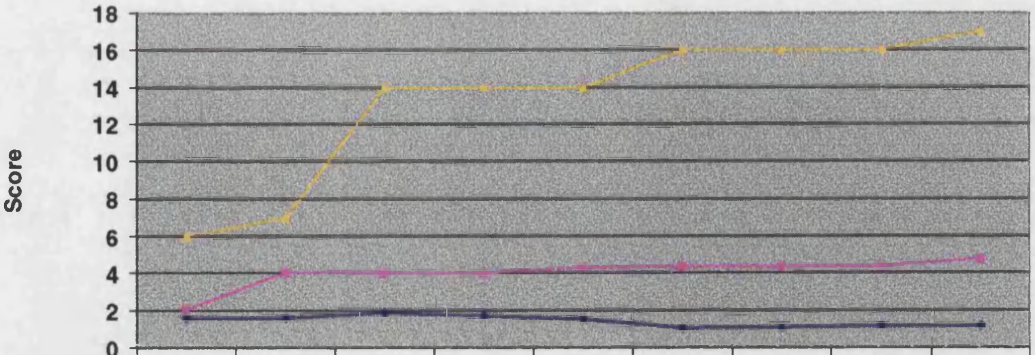
## Patient 9




| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|
| DAS | 2.53 | 2.58 | 1.37 | 2.40 | 1.44 | 2.98 | 2.95 | 2.26 | 2.66 |
| PASI | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Nail | 9 | 4 | 4 | 14 | 8 | 8 | 16 | 13 | 13 |

Visit Number

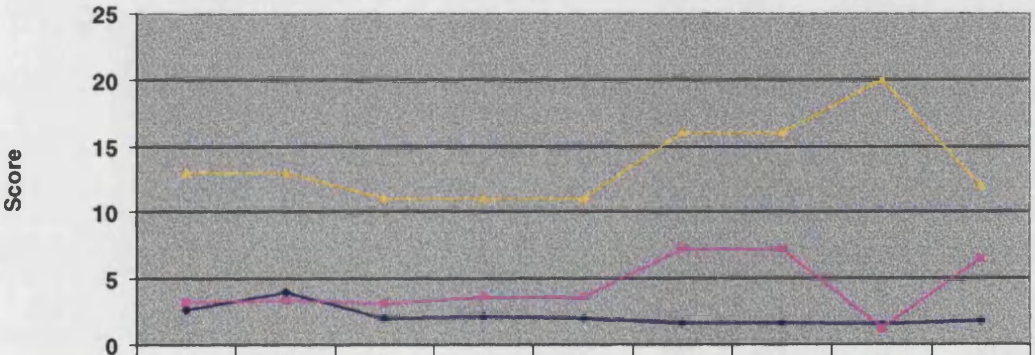
## Patient 10




| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|
| DAS | 1.58 | 1.62 | 1.88 | 1.70 | 1.56 | 1.05 | 1.11 | 1.20 | 1.16 |
| PASI | 2.1 | 4.1 | 4.0 | 4.0 | 4.3 | 4.4 | 4.4 | 4.4 | 4.8 |
| Nail | 6 | 7 | 14 | 14 | 14 | 16 | 16 | 16 | 17 |

Visit Number

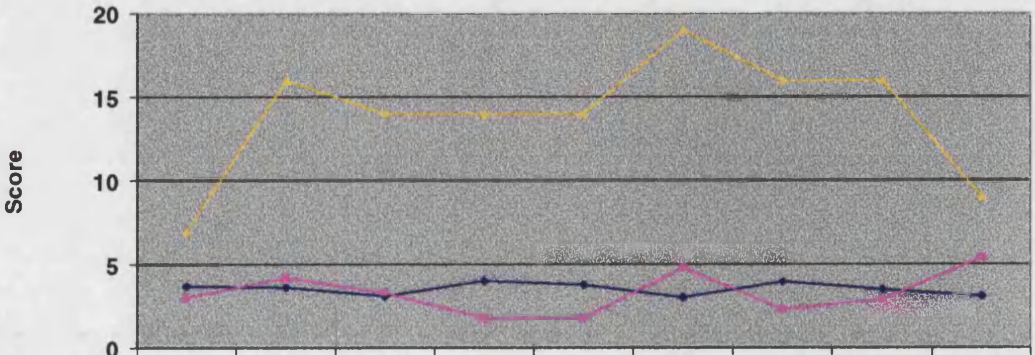
## Patient 11




| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|
| DAS | 2.60 | 3.93 | 1.94 | 2.17 | 2.00 | 1.69 | 1.65 | 1.58 | 1.81 |
| PASI | 3.2 | 3.4 | 3.1 | 3.6 | 3.6 | 7.2 | 7.2 | 1.2 | 6.5 |
| Nail | 13 | 13 | 11 | 11 | 11 | 16 | 16 | 20 | 12 |

Visit Number

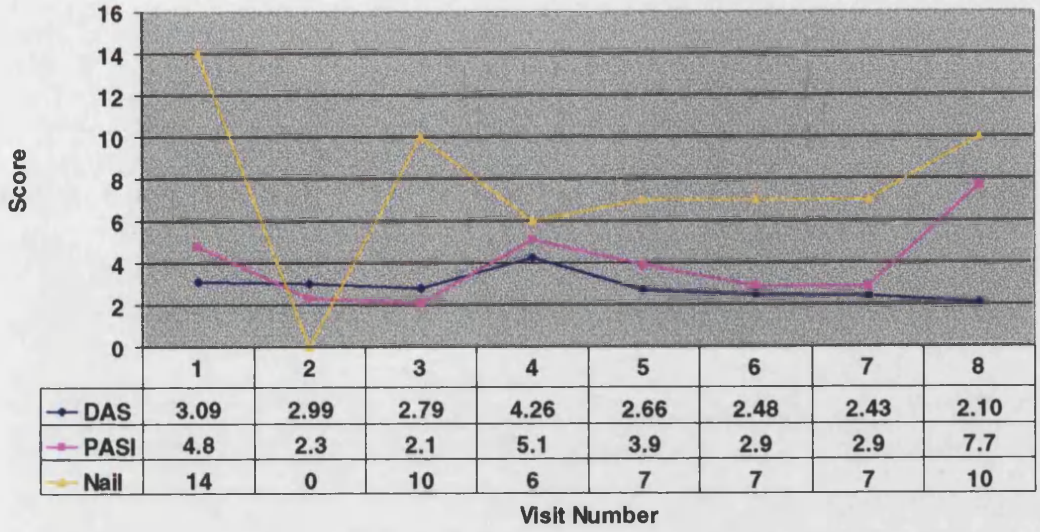
## Patient 12




| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|
| DAS | 3.68 | 3.60 | 3.10 | 4.00 | 3.73 | 3.01 | 3.97 | 3.47 | 3.10 |
| PASI | 3.0 | 4.2 | 3.3 | 1.8 | 1.8 | 4.8 | 2.3 | 2.9 | 5.4 |
| Nail | 7 | 16 | 14 | 14 | 14 | 19 | 16 | 16 | 9 |

Visit Number

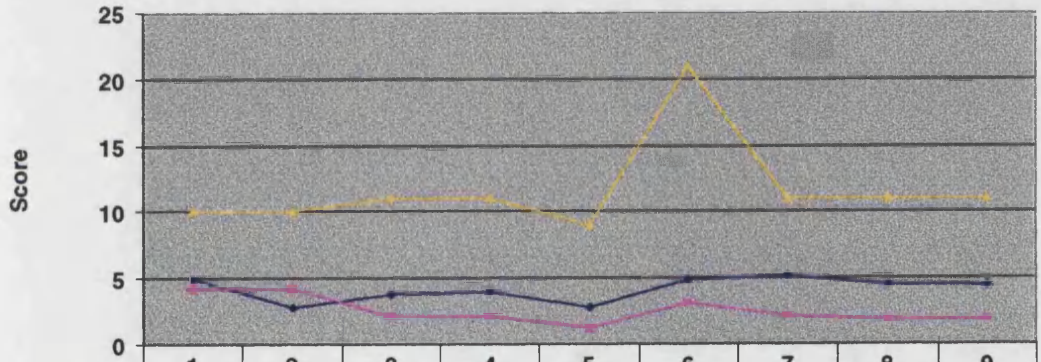
## Patient 13




| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|
| DAS | 3.09 | 2.99 | 2.79 | 4.26 | 2.66 | 2.48 | 2.43 | 2.10 |
| PASI | 4.8 | 2.3 | 2.1 | 5.1 | 3.9 | 2.9 | 2.9 | 7.7 |
| Nail | 14 | 0 | 10 | 6 | 7 | 7 | 7 | 10 |

Visit Number

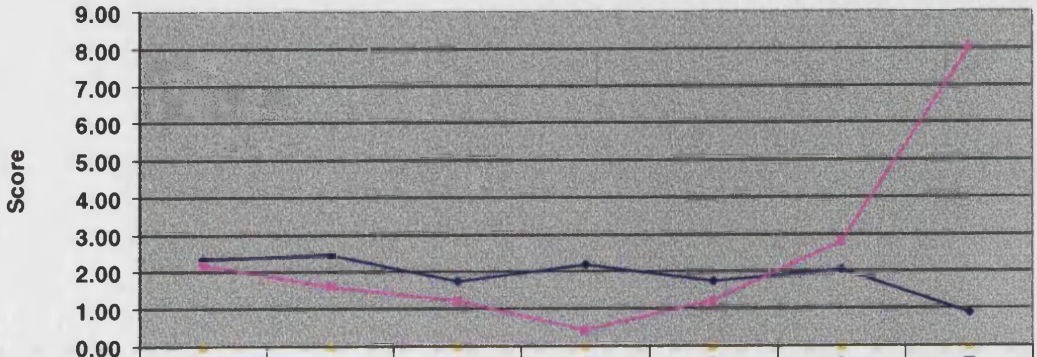
## Patient 14




| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|
| DAS | 4.93 | 2.78 | 3.79 | 3.95 | 2.77 | 4.83 | 5.19 | 4.53 | 4.44 |
| PASI | 4.2 | 4.2 | 2.1 | 2.1 | 1.2 | 3.1 | 2.1 | 1.9 | 1.9 |
| Nail | 10 | 10 | 11 | 11 | 9 | 21 | 11 | 11 | 11 |

Visit Number

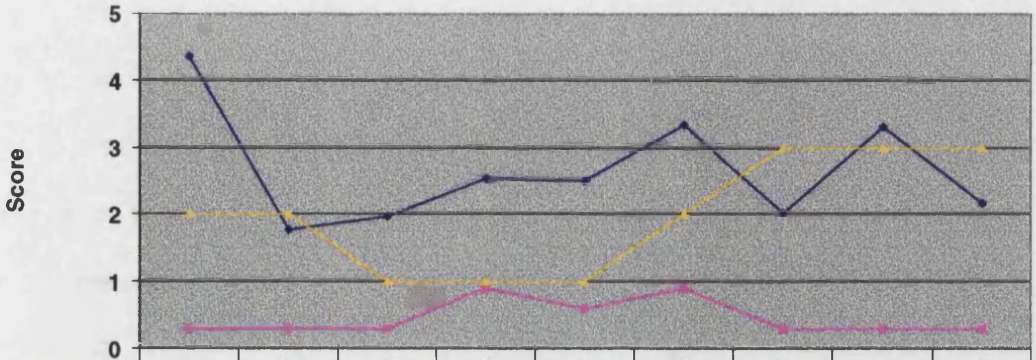
## Patient 15




| | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|
| DAS | 2.33 | 2.45 | 1.76 | 2.20 | 1.75 | 2.03 | 0.89 |
| PASI | 2.2 | 1.6 | 1.2 | 0.4 | 1.2 | 2.8 | 8.0 |
| Nail | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

Visit Number

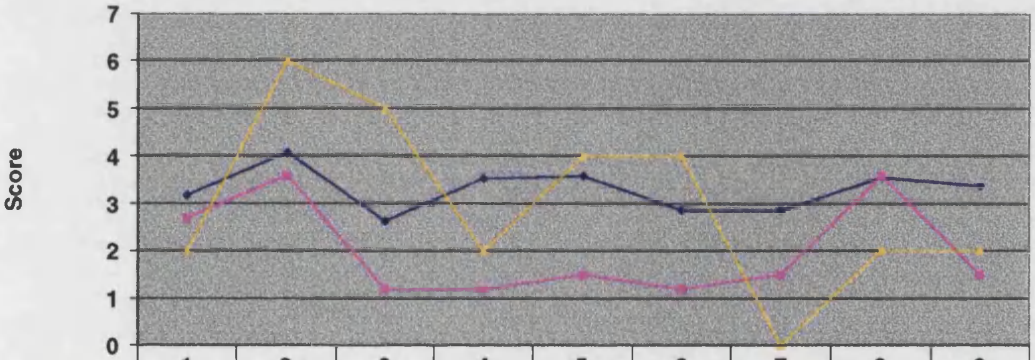
## Patient 16




| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|
| DAS | 4.35 | 1.77 | 1.98 | 2.54 | 2.51 | 3.34 | 2.03 | 3.30 | 2.17 |
| PASI | 0.3 | 0.3 | 0.3 | 0.9 | 0.6 | 0.9 | 0.3 | 0.3 | 0.3 |
| Nail | 2 | 2 | 1 | 1 | 1 | 2 | 3 | 3 | 3 |

Visit Number

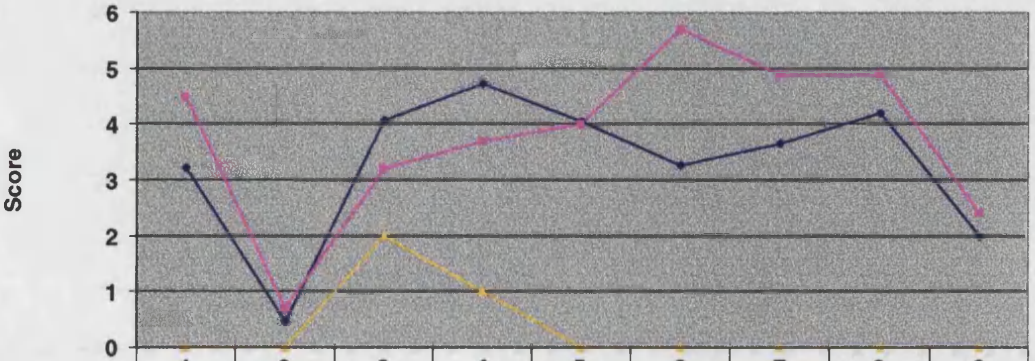
## Patient 17




| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|
| DAS | 3.18 | 4.08 | 2.62 | 3.52 | 3.57 | 2.85 | 2.86 | 3.55 | 3.37 |
| PASI | 2.7 | 3.6 | 1.2 | 1.2 | 1.5 | 1.2 | 1.5 | 3.6 | 1.5 |
| Nail | 2 | 6 | 5 | 2 | 4 | 4 | 0 | 2 | 2 |

Visit Number

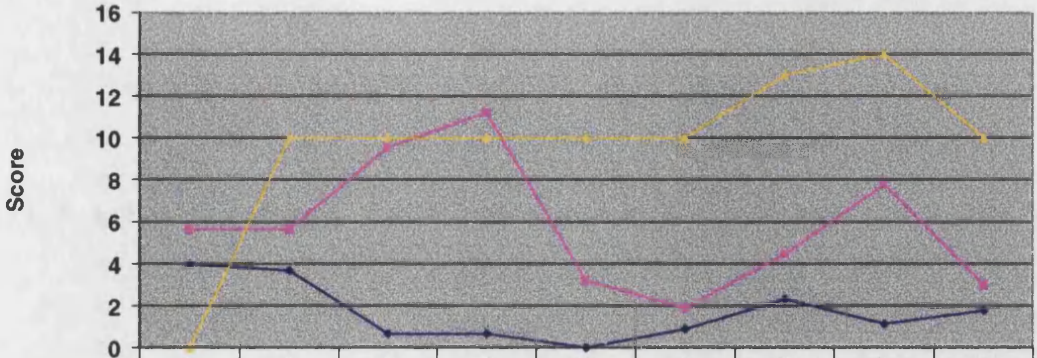
## Patient 18




| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|
| DAS | 3.21 | 0.45 | 4.06 | 4.73 | 4.05 | 3.25 | 3.65 | 4.20 | 1.99 |
| PASI | 4.5 | 0.7 | 3.2 | 3.7 | 4.0 | 5.7 | 4.9 | 4.9 | 2.4 |
| Nail | 0 | 0 | 2 | 1 | 0 | 0 | 0 | 0 | 0 |

Visit Number

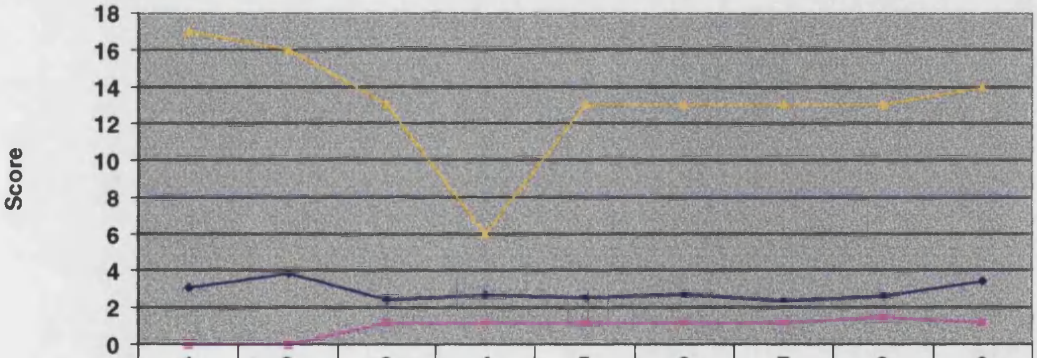
## Patient 19




| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|
| DAS | 4.01 | 3.69 | 0.68 | 0.68 | 0.00 | 0.88 | 2.33 | 1.14 | 1.81 |
| PASI | 5.7 | 5.7 | 9.6 | 11.2 | 3.2 | 1.9 | 4.5 | 7.8 | 3.0 |
| Nail | 0 | 10 | 10 | 10 | 10 | 10 | 13 | 14 | 10 |

Visit Number

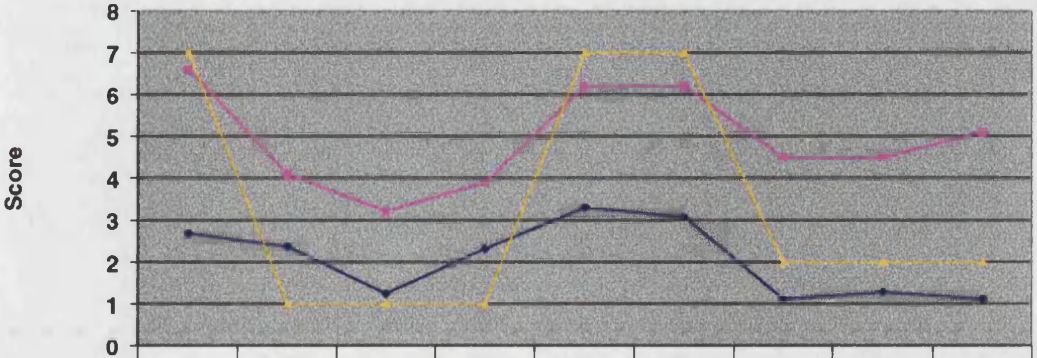
## Patient 20




| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|
| DAS | 3.07 | 3.83 | 2.43 | 2.67 | 2.56 | 2.74 | 2.37 | 2.62 | 3.46 |
| PASI | 0.0 | 0.0 | 1.2 | 1.2 | 1.2 | 1.2 | 1.2 | 1.5 | 1.2 |
| Nail | 17 | 16 | 13 | 6 | 13 | 13 | 13 | 13 | 14 |

Visit Number

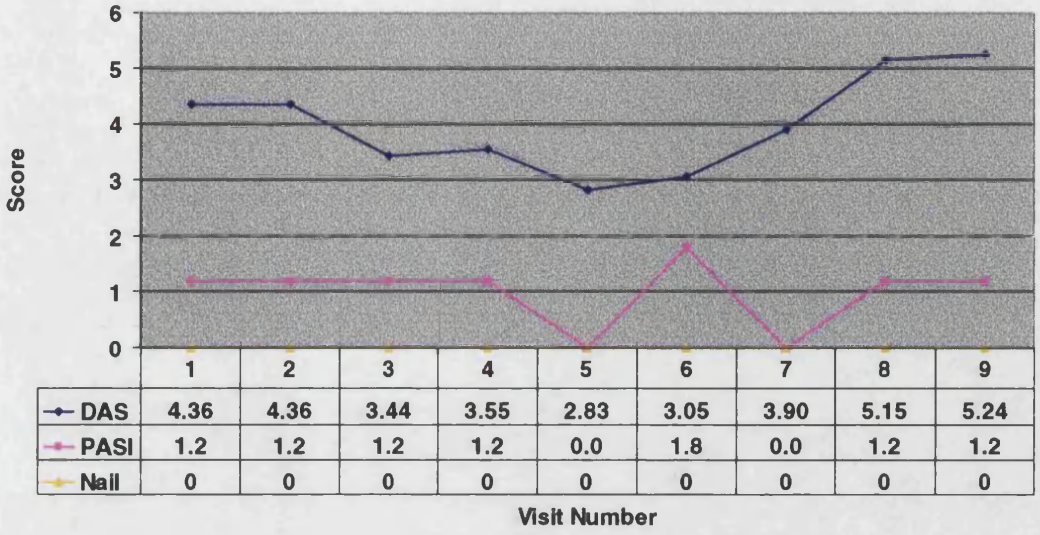
## Patient 21




| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|
| DAS | 2.69 | 2.38 | 1.24 | 2.30 | 3.29 | 3.08 | 1.09 | 1.27 | 1.12 |
| PASI | 6.6 | 4.1 | 3.2 | 3.9 | 6.2 | 6.2 | 4.5 | 4.5 | 5.1 |
| Nail | 7 | 1 | 1 | 1 | 7 | 7 | 2 | 2 | 2 |

Visit Number

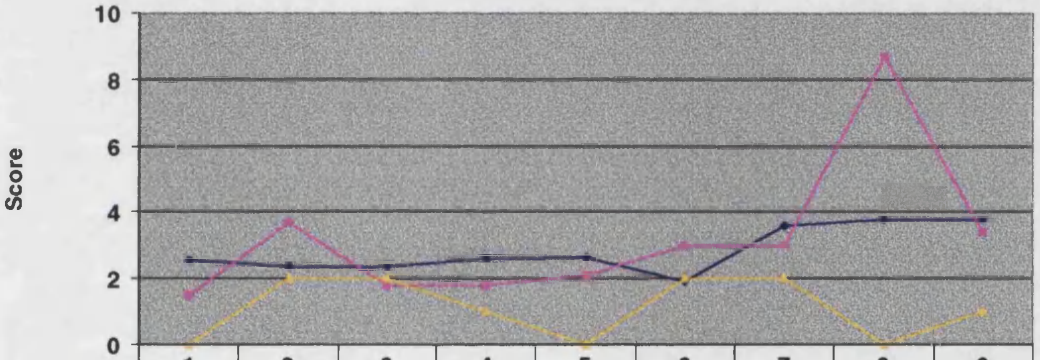
## Patient 22




| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|
| DAS | 4.36 | 4.36 | 3.44 | 3.55 | 2.83 | 3.05 | 3.90 | 5.15 | 5.24 |
| PASI | 1.2 | 1.2 | 1.2 | 1.2 | 0.0 | 1.8 | 0.0 | 1.2 | 1.2 |
| Nail | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

Visit Number

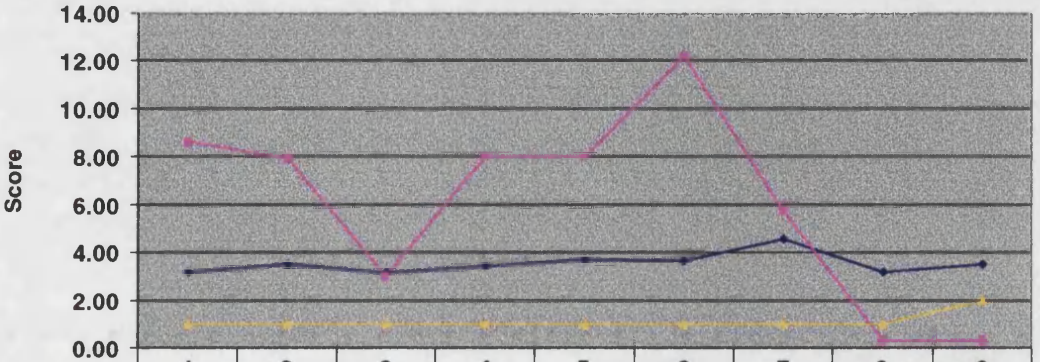
## Patient 23




| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|
| DAS | 2.55 | 2.36 | 2.36 | 2.60 | 2.62 | 1.91 | 3.59 | 3.79 | 3.79 |
| PASI | 1.5 | 3.7 | 1.8 | 1.8 | 2.1 | 3.0 | 3.0 | 8.7 | 3.4 |
| Nail | 0 | 2 | 2 | 1 | 0 | 2 | 2 | 0 | 1 |

Visit Number

## Patient 24




| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|
| DAS | 3.20 | 3.49 | 3.15 | 3.42 | 3.67 | 3.65 | 4.57 | 3.16 | 3.52 |
| PASI | 8.6 | 7.9 | 3.0 | 8.0 | 8.0 | 12.2 | 5.7 | 0.3 | 0.3 |
| Nail | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 |

Visit Number

# APPENDIX E

## ANALYSIS OF SYNOVIAL TISSUE AND SKIN IN PSORIATIC ARTHRITIS

**Information for Patients**

We are investigating the link between skin and joint disease in psoriatic arthritis to try to improve our understanding of the disease which may lead to improvements in treatment in the future.

Synovial tissue is the lining membrane of the joint which becomes inflamed in psoriatic arthritis. We wish to examine the composition of the synovial tissue using new techniques in the laboratory. We also wish to examine the skin in a similar way.

The synovial biopsy involves removing a small piece of synovial tissue by inserting a sharp needle into the knee joint after has been anaesthetised with local anaesthetic. This is a routine procedure frequently used to investigate the type of arthritis. Following the procedure you will be required to rest your knee in the hospital for three hours after which you will be free to go home. If you experience any discomfort after the procedure please contact the hospital. This is uncommon but occasionally bleeding into the joint can cause inflammation.

Skin biopsy involves removing a small piece of skin form an area involved with psoriasis. It is a routine procedure in dermatology and will be performed by a dermatologist. It takes a few minutes.

Participation in this study is entirely voluntary and confidential. Should you feel that you are not able to take part please feel free to say so. This will not affect your continuing or future treatment in any way.

## ANALYSIS OF SYNOVIAL TISSUE IN RHEUMATOID ARTHRITIS

**Information for Patients**

Synovial tissue is the lining membrane of the joint which becomes inflamed in rheumatoid arthritis. We wish to examine the composition of the synovial tissue using new techniques in the laboratory.

The synovial biopsy involves removing a small piece of synovial tissue by inserting a sharp needle into the knee joint after has been anaesthetised with local anaesthetic. This is a routine procedure frequently used to investigate the type of arthritis. Following the procedure you will be required to rest your knee in the hospital for three hours after which you will be free to go home. If you experience any discomfort after the procedure please contact the hospital. This is uncommon but occasionally bleeding into the joint can cause inflammation.

Participation in this study is entirely voluntary and confidential. Should you feel that you are not able to take part please feel free to say so. This will not affect your continuing or future treatment in any way.

**Consent**

The aims and nature of the study have been satisfactorily explained to me and I agree to my participation.

**Patient's Signature:** **Date:**

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**Signature of Witness:** **Date:**

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# APPENDIX F

## PUBLICATIONS AND ABSTRACTS ASSOCIATED WITH THIS THESIS

### PUBLICATIONS

Jones SM, Harris CPD, Lloyd J, Stirling CA, Reckless JPD, McHugh NJ. Lipoproteins and their subfractions in psoriatic arthritis: identification of an atherogenic profile with active joint disease. (Submitted)

Jones SM, Dixey J, Hall ND, McHugh NJ. Expression of the cutaneous lymphocyte antigen (CLA) and its counter-receptor E-selectin in the skin and joints of patients with psoriatic arthritis. British Journal of Rheumatology 1997 36;7: 748-757.

Jones SM, Armas JB, Cohen MG, Lovell CR, Evison G, McHugh NJ. Psoriatic arthritis: Outcome of disease subsets and relationship of joint disease to nail and skin disease. British Journal of Rheumatology 1994. 33; 9: 834-839.

Jones SM, McHugh NJ. Subgroups in psoriatic arthritis. British Journal of Rheumatology 1994. (L) 33;8:789.

### PAPERS IN PREPARATION

Jones SM, Balachrishnan C, Evison G, McHugh N J. Outcome in psoriatic arthritis - a prospective 5 year clinical and radiological follow-up study

Jones SM, McHugh NJ. The temporal relationship between joint, skin and nail disease - a prospective 2 year study

Jones SM, Magaro L, McHugh NJ. The influence of hormonal factors on the onset and course of psoriatic arthritis.

Balachrishnan C, Jones SM, Evison G, McHugh N J. Validation of a modified sharp's index for the hands in psoriatic arthritis.

Dixey J, Jones SM, Cox B, Hall ND, McHugh NJ. Prevalence of the HLA DRB1 'shared epitope' in psoriatic arthritis and relationship to patterns and progression of disease

**PUBLISHED ABSTRACTS**

Jones SM, Magaro L, McHugh NJ. The influence of hormonal factors on the onset and course of psoriatic arthritis. British Journal of Rheumatology 1997. 26; Suppl 1: 133.

Balakrishnan C, Jones S M, McHugh N J. Sharp's index modified for psoriatic arthritis: a five year follow-up study of hand radiology. Arthritis and Rheumatism 1996 39;9: S207.

Jones S M, Balachrishnan C, Dixey J, Flora R and McHugh N J. Progression of peripheral joint disease and prevalence of the HLADRB1 "shared epitope" in psoriatic arthritis. Arthritis and Rheumatism 1996 39;9: S204.

Jones S M, Balakrishnan C, McHugh N J. Progression of peripheral joint disease in psoriatic arthritis: a five year clinical follow-up study. British Journal of Rheumatology 1996 35; Suppl 1: 158.

Balakrishnan C, Jones S M, Evison G, McHugh N J. Hand radiology in psoriatic arthritis: a five year follow up study. British Journal of Rheumatology 1996 35; Suppl 1: 158.

Flora R S, Jones S M, Balakrishnan C, Hall N D, McHugh N J. Prevalence of the rheumatoid arthritis "shared epitope" in patients with psoriatic arthritis. British Journal of Rheumatology 1996; Suppl 1: 159.

Jones SM, Dixey J, Hall ND, McHugh NJ. Cutaneous lymphocyte antigen (CLA) expression in the skin and joints of psoriatic and rheumatoid arthritis. Arthritis and Rheumatism 1994. 37;6:S206.

Jones SM, Armas J, Lovell CR, McHugh NJ. Outcome of disease subsets and relationship to distal interphalangeal joint disease in 100 patients with psoriatic arthritis. Arthritis and Rheumatism 1994. 37;6:S206.

Jones SM, Lloyd J, Barnes J, Stirling CA, Harris CPD, Reckless JPD, McHugh NJ. Lipoproteins and their subfractions in psoriatic arthritis. Arthritis and Rheumatism 1994. 37;6:S206.

Jones SM, Dixey J, Hall ND, McHugh NJ. Cutaneous lymphocyte antigen expression in the skin and joints of psoriatic and rheumatoid arthritis. British Journal of Rheumatology 1994. 33; Suppl 2: 9.

Jones SM, J Armas J, Lovell CR, McHugh NJ. Outcome of disease subsets and relationship to distal interphalangeal joint disease in 100 patients with psoriatic arthritis. British Journal of Rheumatology 1994. 33 (Suppl 1):128 (poster discussion).

Jones SM, Lloyd J, Barnes J, Sterling CA, Harris CPD, Reckless JPD, McHugh NJ. Lipid profiles in 50 patients with psoriatic arthritis and their age and gender matched controls. British Journal of Rheumatology 1994. 33 (Suppl 1):128.

Jones SM, Stirling CA, Leong KH, Lloyd J, Quinn L, Harris CPD, Reckless JPD, McHugh NJ. Lipoprotein (a) in SLE and psoriatic arthritis. British Journal of Rheumatology 1994. 33 (Suppl 1):129.

Harris CPD, Jones SM, Lloyd J, Stirling CA, Reckless JPD, McHugh NJ. Lipoprotein subfractions by ulracentrifugation in 13 patients with psoriatic arthritis. British Journal of Rheumatology 1994. 33 (Suppl 1):129.

Jones SM, Armas J, Lovell CJ, McHugh NJ. Nail and skin disease in psoriatic arthritis. British Journal of Rheumatology 1993. 32: Suppl 1: 62: 19.

Jones SM, Armas J, Lovell CJ, Evison G, McHugh N J. Patterns of disease in psoriatic arthritis. Rev Esp Rheumatol 1993: Vol. 20, Suppl 1: 482; FR7.

**ORAL PRESENTATIONS**

S M Jones. Results and review of five year follow-up study in psoriatic arthritis. Psoriatic Alliance 2nd Annual General Meeting, September 1996.

S M Jones. Studies of Psoriatic Arthritis. Psoriatic Alliance Inaugural Meeting, September 1995.

S M Jones, J Lloyd, J Barnes, CA Sterling, CPD Harris, JPD Reckless, NJ McHugh. Lipid profiles in psoriatic arthritis. South West, Wales and Wessex Rheumatology Club Meeting, May 1994.

S M Jones, N J McHugh. Treatment of psoriatic arthritis and relationship to disease subsets in 101 patients. Proceedings of the fifth International Symposium on the treatment of psoriasis and psoriatic arthritis, Israel, March 1994.

*British Journal of Rheumatology* 1994;**33**:834–839

# PSORIATIC ARTHRITIS: OUTCOME OF DISEASE SUBSETS AND RELATIONSHIP OF JOINT DISEASE TO NAIL AND SKIN DISEASE

**S. M. JONES,* J. B. ARMAS,* M. G. COHEN,* C. R. LOVELL,† G. EVISON† and N. J. McHUGH***

**Royal National Hospital for Rheumatic Diseases, Upper Borough Walls, Bath BA1 1RL and †Royal United Hospital, Bath*

## SUMMARY

Subgroups of PsA have been described but their relationship to the mode of onset of arthritis, to DIP joint disease and to nail and skin disease remains controversial. Therefore, the pattern of disease was documented in 100 patients with PsA in whom the mode of onset was known. The patients were divided into six subgroups: monoarthritis; DIP joint disease only; oligoarthritis; polyarthritis; spondyloarthropathy and arthritis mutilans. Sixty-four patients changed pattern. Nail disease (67% of total) was more common in patients with DIP joint disease (27% of total) and was significantly associated with adjacent DIP joint disease. Skin and nail disease severity did not correlate with joint severity, joint activity or functional status, nor differ between subgroups. Therefore, the mode of onset does not predict outcome in the majority. The topographic association of nail disease and involvement of the adjacent DIP joints suggests a common local inflammatory mechanism.

KEY WORDS: Arthritis, Psoriasis, Nail dystrophy, Spondyloarthropathy, Classification.

THE assocation between psoriasis and joint disease was first recognized by Alibert in 1818 [1] although radiographic evidence of PsA has been observed in medieval skeletons [2]. Despite its antiquity, the distinction of PsA from RA and its relationship to the seronegative spondyloarthritides have remained a subject for debate. The absence of RF in the majority of patients with psoriasis and arthritis led to recognition of PsA as a distinct entity [3]. The discovery that RA improves with the depletion of T helper lymphocytes secondary to HIV infection, whereas psoriasis or psoriatic arthropathy get worse [4, 5] supports this distinction. Family studies were important in establishing the concept of the seronegative spondyloarthritides [6], which share common clinical features and have an increased frequency of HLA B27 [7, 8]. However PsA has unique features which includes the predominance of a characteristic peripheral arthropathy and a spondyloarthropathy which differs radiologically from AS. In addition, HLA B27 is present in less than 50% of patients.

PsA has been divided into subgroups according to the distribution and number of joints involved [9]. It is unclear whether these subgroups are homogenous with time [10, 11]. Also, relatively few series of patients hvae been reported in which the relationship between the skin, nails and joints has been adequately studied, particularly in relation to the topographic association of nail and skin disease. In the present study we have investigated whether the mode of onset of joint disease predicts the ultimate pattern of disease expression. We have also assessed in detail the relationship between nail and DIP joint disease, and patterns of skin and nail involvement in relation to the severity, activity and subgroups of joint disease.

Received 21 February; revised version accepted 16 May 1994.

## PATIENTS AND METHODS

In 1986 a clinic was established at the Royal National Hospital for Rheumatic Diseases, Bath to study joint disease in patients with psoriasis. We present a cross-sectional study of the first 100 patients to attend this clinic in whom the mode of onset was known. All patients had an inflammatory arthropathy and psoriasis. The presence of RF was not used as an absolute exclusion criterion because of its lack of specificity for RA and its low prevalence in the normal population. The majority of patients were referrals from other rheumatology clinics, some were new referrals from the general practitioner and a minority (less than 10%) were referrals from dermatology clinics. All patients were seen by a rheumatologist (NJM) and data were accumulated using a specially designed form.

The age of onset and the duration of psoriasis and arthritis, the family history, the mode and site of onset of joint disease and previous and current treatment were recorded. The mode of onset referred to the joints involved within the first 3 months of symptoms. This information was usually well recalled by the patient and in most cases confirmed by documentation in the rheumatology case notes. However, we acknowledge that the absence of a complete record of objective clinical findings at onset may have resulted in an underestimate of the number and site of joints involved, particularly if some joints were significantly more severely involved than others. Conversely, some patients may have over estimated the number of involved joints if there was pain without objective clinical findings. The initial presentation was subdivided using three methods. Firstly five groups were identified; monoarthritis, DIP joint disease only, oligoarthritis (two to four joints affected), polyarthritis (five or more joints affected), and spinal disease. Secondly, the

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patients were divided by joint size into small joint (including hands and feet), large joints of the limbs, axial (including the spine and chest wall), and combinations of these. Thirdly, the patients were divided by anatomical region into upper limb, lower limb, spinal disease and combinations of these.

Peripheral and axial joint involvement was documented for each patient. The number of active joints was documented by a modified Ritchie index (to include DIP joints). An index of peripheral joint disease severity was obtained by counting the number of peripheral joints involved either clinically or radiologically and assessed as mild (fewer than 10 joints), moderate (10–20 joints) or severe (>20 joints). The pattern of joint disease was analysed in a similar way to the mode of onset with the addition of arthritis mutilans as a sixth subgroup. Although symmetry was not used to distinguish subgroups, symmetrical joint involvement was defined in two ways; firstly by at least one identical joint being involved on both sides of the body and secondly in a method devised by Helliwell *et al.* [11]. In the latter method, the number of matched pairs of involved joints was related to the total number of matched and unmatched pairs and a ratio of 0.5 or greater defined symmetry. Functional assessment was made using the Stanford Health Assessment Questionnaire (HAQ) [12, 13].

The skin and nails were examined using a predefined protocol and performed under the supervision of a dermatologist (CL). Psoriasis was classified as plaque (psoriasis vulgaris), discoid, guttate, localized pustular or a combination of these. The distribution of skin psoriasis was recorded and the current severity was graded according to the Psoriasis Area and Severity Index (PASI) score (range 0 to 72) [14]. A nail score was determined for each patient, and derived as follows. Each fingernail was assessed for pitting, onycholysis, hyperkeratosis and severe nail deformity with involvement of both sides of the nail ('dystrophy'). Each of the listed features scored one with a possible maximum nail score of 40.

Radiological evaluation was performed on clinically affected joints. The radiological protocol consisted of an anterior-posterior (AP) view of both hands and feet, lateral view of both heels, AP view of pelvis, AP view of lumbar spine (to include thoraco-lumbar junction) and a lateral view of the cervical spine in flexion. All films were examined by a radiologist (GE) and by a rheumatologist (NJM). The detailed radiology of peripheral joints, axial and sacro-iliac joints will be reported elsewhere.

TABLE I
Clinical features in 100 patients with PsA

| | |
|---|---|
| No. of females | 57 |
| No. of males | 43 |
| Mean age (yr) (range) | 49.7 (16–80) |
| Mean age at onset of skin lesions (yr) (range) | 28.9 (3–70) |
| Mean age of onset of joint disease (yr) (range) | 37.6 (5–70) |
| Psoriasis before arthritis | 63 |
| Simultaneous onset | 19 |
| Arthritis before psoriasis | 18 |
| Mean duration of psoriasis (yr) (range) | 20.8 (1–61) |
| Mean duration of arthritis (yr) (range) | 12.1 (1–53) |
| Family history of psoriasis | 39 |
| Nail lesions | 67 |
| Iritis | 5 |

All information was entered on an Apple Macintosh computer. Statistical analysis was performed using standard software packages. The $\chi^2$ test was used for comparing discrete variables between subgroups and Student's *t*-test for comparing continuous variables for parametric data; the Mann–Whitney U test was used for non-parametric data. Spearman's rank coefficient was used for correlation analysis.

## RESULTS

### *Clinical characteristics*

*Age and sex distribution of psoriasis and arthritis.* The general characteristics of the study group including the age and sex distribution are given in Table I. Ninety-nine were seronegative for RF (less than 80 IU by nephelometry).

*Mode of onset and outcome of disease subsets.* The outcome of disease in relation to the mode of onset is summarized in Table II. Ninety per cent of 39 patients presenting with a monoarthritis, 79% of 24 patients with an oligoarthritis and 20% of 25 patients with a polyarthritis changed pattern. Six of 10 patients presenting with spinal symptoms developed a spondyloarthropahy. In total, 64 patients changed pattern, 62 of whom had progression of their disease. Of the four patients who remained in the monoarthritis group three had involvement of one knee and one had disease confined to a single PIP joint. Two patients had apparent regression of their disease with a polyarthritis at onset and subsequently only evidence of an oligoarthritis. Four patients who presented with spinal symptoms developed a peripheral arthritis without spondyloarthropathy.

The distribution of the site and the type of joint disease at onset are shown in Table III. Fifty-three patients presented with small joint disease which was more frequent in females ($P<0.01$) as was upper limb disease at onset ($P<0.05$). Thirty-one of these (24 females, seven males, $P<0.01$) presented with hand disease which was the most common site of onset. Axial onset was more frequent in males ($P<0.01$) and those presenting with spinal disease were significantly younger (mean age 41.8 yr, S.D. 6.9) than the oligoarthritis (mean 47.9 ± 14.7) ($P<0.05$) or polyarthritis (mean 50.5 ± 15.0 yr) ($P<0.02$) groups. The mean ages for the monoarthritis and mutilans groups were 48.2 ± 12.1 yr and 59.0 ± 16.0 yr respectively.

Only one patient, included in the oligoarthritis group, had the synovitis acne pustulosis hyperostosis osteomyelitis syndrome (SAPHO) [15]. Table IV shows the disease duration, HAQ scores and use of DMARDs of the subgroups. Not unexpectedly, the polyarthritis group had a significantly worse functional outcome defined by HAQ scores than the oligoarticular and monoarthritis groups combined ($P<0.05$) and had also used more disease-modifying therapy ($P<0.01$), had a longer disease duration ($P<0.01$) and

TABLE II
Evolution of disease subsets

| Mode of onset | Outcome | | | | | | Total |
|---|---|---|---|---|---|---|---|
| | Mono | DIP | Oligo | Poly | Spond | Arthritis mutilans | |
| Monoarthritis (mono) | 4 | 0 | 13 | 22 | 0 | 0 | 39 |
| DIP joint disease only | 0 | 1 | 1 | 0 | 0 | 0 | 2 |
| Oligoarthropathy (oligo) | 0 | 0 | 5 | 18 | 0 | 1 | 24 |
| Polyarthropathy (poly) | 0 | 0 | 2 | 20 | 0 | 3 | 25 |
| Spondyloarthropathy (spond) | 0 | 0 | 1 | 3 | 6 | 0 | 10 |
| | 4 | 1 | 22 | 63 | 6 | 4 | 100 |

more erosions ($P<0.001$) than the oligoarticular group. Of those with peripheral arthritis, patients with more severe disease had longer disease durations. Those with arthritis mutilans had the longest disease duration followed by polyarthropathy, with the monoarthritis/DIP joint disease only and oligoarthropathy groups having the shortest disease durations.

The frequency of symmetry depended on the method employed. When only one identical contralateral joint was required to define symmetry, all 63 of the polyarthritis group and six of 22 of the oligoarthritis group had symmetrical disease. When Helliwell's method was used, 51 of 63 patients in the polyarthritis group and four of 22 patients in the oligoarthritis group had symmetrical disease.

*Relationship between joint disease and skin and nail involvement.* The distribution of the specific types of skin and nail disease are shown in Table V. This distribution is similar to that in the general psoriatic population [16]. There was no association between the type or distribution of skin involvement and arthritis subgroup, nor was there any relationship between the activity of psoriasis and joint severity, activity or functional status. However, there was a significant correlation between the number of involved joints (joint score) and functional status (HAQ score). There was a significant correlation between PASI and the nail scores ($P<0.001$) and nail disease increased with the duration of psoriasis ($P<0.02$) (Table VI).

Sixty-seven per cent of patients had psoriatic nail disease, which is a greater frequency than that found in psoriasis alone and reflects that found in previous studies [17]. All patients with hyperkeratosis or 'dystrophy' had either pitting, onycholysis or both. The nail score was significantly greater in those who developed psoriasis before arthritis or simultaneously ($P<0.05$). Nail disease occurred in all subgroups (Table III). There was no correlation between nail severity and the severity of arthritis. Males tended to have more severe skin and nail disease than females, but this was not significant.

TABLE III
Type and site of joint disease at onset by sex

| Joint disease | M | F | Significance | Total |
|---|---|---|---|---|
| Small | 18 | 35 | ($P<0.01$) | 53 |
| Large | 12 | 17 | (N.S.) | 29 |
| Lower limb | 18 | 24 | (N.S.) | 42 |
| Upper limb | 11 | 27 | ($P<0.05$) | 38 |
| Axial | 9 | 1 | ($P<0.01$) | 10 |
| Small and large | 3 | 4 | (N.S.) | 7 |
| Small and axial | 1 | 0 | (N.S.) | 1 |
| Spinal and peripheral disease | 1 | 0 | (N.S.) | 1 |
| Upper and lower limb | 6 | 3 | (N.S.) | 9 |

Twenty-seven per cent of patients had clinical or radiological evidence of DIP joint disease in their hands which is less than in other series [18]. Those with DIP joint disease tended to have a longer disease duration than those without (means 15.6 and 11.0 yr respectively) but this was not significant. DIP joint disease occurred in all subgroups except spondyloarthropathy and monoarthritis, but only one patient had DIP joint disease exclusively (Table III).

Nail disease was more common in patients with DIP joint involvement (85 *vs* 60%) ($P<0.02$). Patients with nail disease in a specific digit were significantly more likely to have DIP disease in the adjacent joint than those without nail disease in that digit ($P<0.001$). Patients with nail disease on one side were also more likely to have DIP disease on the same side than those with no nail disease on that side ($P<0.05$). Patients with DIP joint disease also tended to have more severe nail disease, but this did not reach significance.

## DISCUSSION

Attempts to classify PsA have been complicated by the overlap between subgroups, the importance given to extraosseus abnormalities, including the SAPHO syndrome [15], the definition of symmetry, the relationship of DIP joint disease to the subgroups and the temporal change in the pattern of arthritis.

Moll and Wright, based on their own descriptive work [19–22] and radiological studies by Avila *et al.* [23] described five clinical patterns: (i) 'classic' PsA confined to DIP joints of hands and feet (5%); (ii) arthritis mutilans with sacro-iliitis (5%); (iii) symmetric polyarthritis, indistinguishable from RA (15%); (iv) asymmetric oligoarthritis (70%); and (v) spondyloarthropathy (5%) [24]. Further studies and review articles reaffirmed these subgroups [9, 25–30], although the overlap between subgroups and possible evolution from one subgroup to another was noted [31]. A more recent study using radionucleotide scanning concluded that all patients with peripheral arthritis should be grouped together, the spondyloarthropathy group retained and a new group added, comprising rare patients with extra-articular osseous disease, including patients with SAPHO [11].

TABLE IV
Pattern of joint disease by disease duration, HAQ score, use of DMARDs and nail and DIP joint disease

| Subgroup | No. of patients | Sex M | Sex F | Mean duration arthritis (yr) | Mean duration psoriasis (yr) | Mean HAQ score | Use of DMARDs (% subgroup) | Nail disease (% subgroup) | DIP disease (% subgroup) |
|---|---|---|---|---|---|---|---|---|---|
| Monoarthritis (mono) | 4 | 1 | 3 | 6.8 | 24.8 | 0.41 | 0 | 3 (75) | 0 |
| DIP joint disease only | 1 | 1 | 0 | 10 | 10 | 0.125 | 0 | 1 (100) | 4 (100) |
| Oligoarthropathy (oligo) | 22 | 8 | 14 | 6.6 | 14.5 | 0.49 | 9.1 | 13 (59) | 3 (9) |
| Polyarthropathy (poly) | 63 | 25 | 38 | 13.9 | 20.2 | 0.87 | 50.8 | 45 (71) | 19 (30) |
| Spondyloarthropathy (spond) | 6 | 6 | 0 | 13.7 | 19.5 | 0.65 | 33 | 2 (33) | 0 |
| Arthritis mutilans (AM) | 4 | 1 | 3 | 21.5 | 30 | 1.34 | 75 | 3 (75) | 4 (100) |
| Total | 100 | 43 | 57 | 12.5 | 20.6 | 0.77 | 40 | 67 | 27 |

Subgroup comparisons: duration of PsA: poly *vs* oligo (*t*-test), $P = 0.007$; oligo *vs* spond, $P = 0.038$ HAQ score: poly *vs* oligo + mono (*t*-test), $P<0.05$; use of DMARDs: poly *vs* oligo ($\chi^2$ test), $P<0.01$.

Applying this classification to our patients, 94 were grouped together, six remained in the spondylarthritis group and only one belonged to the extra-articular osseous group. Radionucleotide scanning may have revealed more patients with extra-articular osseous abnormalities, but this is not practical in a clinical setting. Whilst the extra-articular osseus group including SAPHO should be recognized, its relative rarity makes its separate classification difficult to justify, a point also made by Veale *et al.* [32]. Other attempts at reclassification include that by Gladman *et al.* who initially increased the number of groups to seven [33], but later in a review of 220 patients, proposed a spectrum of disease patterns and severity [10]. Most recently three groups have been suggested [32], similar to those proposed by Kammer *et al.* [34], with the spondyloarthropathy group retained and peripheral arthritis divided into two subgroups: asymmetric arthritis and symmetric polyarthritis. The groups are loosely defined in terms of the assessment of symmetry and the number of joints involved, but the classification may prove useful clinically.

We have divided our patients into six subgroups: monoarthritis; DIP joint disease alone; oligoarthritis; polyarthritis; spondyloarthritis and arthritis mutilans. The three patients with monoarthritis would be included in Moll and Wright's asymmetrical oligoarticular subgroup, but the lack of progression of disease beyond one knee and the absence of DIP disease distinguished them from the rest of the subgroups. The mean disease duration for the monoarthritis subgroup was similar to that of the oligoarthritis subgroup but about half of the mean for all patients, so it is possible that the patients in these subgroups may have progression of their disease and change subgroup. It is striking that, for those with peripheral arthritis, those with more extensive and severe joint involvement (arthritis mutilans and polyarthropathy groups) had longer disease durations than the DIP joints disease only, oligoarthritis and monoarthritis groups. This raises the possibility that the number of joints involved is a function of disease duration. The homogeneity of the spondyloarthropathy group in this study, with all six patients presenting with spinal symptoms and the absence of DIP joint disease, supports the view that this subgroup should be retained [11, 32].

The subgroup frequencies initially reported by Moll and Wright, who found a majority of patients in the asymmetrical oligoarticular group has not been confirmed in other series. In our study, the ratio of oligoarthritis (including monoarthritis patients to make studies comparable) to polyarthritis was 1 to 2.3. Gladman *et al.* found that oligoarthritis was far less common than polyarthritis with a ratio of 1:2.2 [33] and the preponderance of patients with polyarthritis has subsequently been confirmed by Wright [9]. However, in a recent study of 100 patients, Veale *et al.* found the asymmetrical oligoarthritis subgroup most common, although 11 patients with an asymmetrical polyarthritis were included in this group [32]. When these patients were included in the polyarthritis group, the ratio of oligoarthritis to polyarthritis was 1.0:1.1.

The use of both the number of joints involved and

TABLE V
Pattern of psoriasis and nail disease

| Type of psoriasis | (%) | Type of nail disease | (%) |
|---|---|---|---|
| Plaque | 79 | Pitting | 74 |
| Scalp | 70 | Onycholysis | 70 |
| Discoid | 10 | Hyperkeratosis | 34 |
| Guttate | 4 | Severe nail deformity | 5 |
| Pustular | 3 | ('dystrophy') | |

TABLE VI
Joint, skin and nail correlations

| Parameters | Spearman correlation coefficient | Significance |
|---|---|---|
| Joint score *vs* HAQ | 0.458 | <0.001 |
| Joint score *vs* nail score | 0.12 | N.S. |
| Joint score *vs* PASI | −0.029 | N.S. |
| Joint score *vs* joint activity | −0.033 | N.S. |
| HAQ *vs* nail score | −0.103 | N.S. |
| HAQ *vs* PASI | −0.022 | N.S. |
| PASI *vs* nail | 0.361 | <0.001 |
| PASI *vs* active joints | 0.053 | N.S. |
| Nail *vs* active joints | 0.131 | N.S. |
| HAQ *vs* active joints | −0.046 | N.S. |
| Nail score *vs* duration psoriasis | 0.26 | 0.013 |

HAQ, Stanford Health Assessment Questionnaire; PASI, Psoriasis Area and Severity Index score.

symmetry to define the oligoarticular and polyarticular subgroups has proved difficult in other series [34, 35]. Obviously, the fewer joints involved, the more likely the disease is to be asymmetrical but a small number of patients will inevitably have a symmetrical oligoarthritis or an asymmetrical polyarthritis. The difficulty is illustrated by the differing results of the two methods employed in this study and we therefore did not use symmetry to define our subgroups.

The rarity of pure DIP joint involvement and its occurrence over the spectrum of disease patterns has been previously noted [32, 36]. In our series DIP joint disease occurred in all subgroups except spinal disease and the monoarthritis group, and three patients had DIP joint involvement exclusively. The association of DIP joint disease with nail disease in the same digit has long been recognized, although detailed analysis has not been performed. This study confirms that there is a topographical association of nail disease with DIP joint disease when analysed for each digit and for each hand.

The evolution of disease patterns from oligoarthritis to polyarthritis group is a further matter of debate. Whereas Gladman has suggested that this is common [37], Helliwell *et al.* found that only 5% changed pattern [11]. In this study, 64% of patients presenting with monoarticular or oligoarticular disease developed polyarthritis. It could be argued that the patients changed pattern early in the course of their disease before reaching a plateau, although the significantly greater disease duration for the polyarthritis group suggests that the number of joints involved is a function of disease duration. We have embarked on a long-term prospective study of patients attending the clinic to further evaluate the evolution of disease between subgroups.

Although the attempts to define clinical subgroups of joint disease have added greatly to our clinical perception of PsA, it has had limited impact on our understanding of the pathogenesis. The lack of any serological markers for the disease, adds to this difficulty. In addition, there are no clearcut HLA associations related to specific subgroups of joint or skin disease, although the association of the class II antigens HLA-DR7 to peripheral disease and HLA-DR4 with erosive disease requires further elucidation [38]. The association of nail disease and DIP joint disease is possibly the only clinical evidence that there is a peripheral biological link between events in the skin and the joint. Research into disease mechanisms at a genetic and cellular level is needed to elucidate the true relationship between psoriatic skin, nail and joint disease.

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REFERENCES

1. Alibert JL. *Précis théoretique et pratique sur les maladies de la peau.* Paris: Caille et Ravier; 1818:21.
2. Rogers J, Watt I, Dieppe P. Arthritis in Saxon and mediaeval skeletons. *BMJ* 1981;**283:**1668–70.
3. Blumberg BS, Bunin JJ, Calkins E, Pirani CL, Zafler NJ. ARA nomenclature and classification of arthritis and rheumatism (tentative). *Arthritis Rheum* 1964;**7:**93–7.
4. Espinoza LR, Berman A, Vasey FB *et al.* Psoriatic arthritis and acquired immunodeficiency syndrome. *Arthritis Rheum* 1988;**21:**1034–40.
5. Arnett FC, Revielle JD, Duvic M. Psoriasis and psoriatic arthritis associated with HIV infection. *Rheum Dis Clin N Am* 1991;**17:**59–78.
6. Moll JMH, Haslock I, Macrae IF, Wright V. Association between ankylosing spondylitis, psoriatic arthritis, Reiters disease, the intestinal arthropathies and Behçets syndrome. *Medicine (Baltimore)* 1974;**53:** 343–64.
7. Eastmond CJ, Woodrow JC. The HLA system and the arthropathies associated with psoriasis. *Ann Rheum Dis* 1977;**36:**122–20.
8. Wright V, Moll JMH. Psoriatic arthritis. In: *Sero-negative polyarthritis.* Amsterdam: North Holland; 1976:169–223.
9. Wright V. *Psoriatic Arthritis* ARC *Reports on Rheumatic Diseases (Series 2) Topical Reviews*, May 1992:No. 21.
10. Gladman DD, Shuckett R, Russell ML *et al.* Psoriatic arthritis (PSA)—an analysis of 220 patients. *Q J Med* 1987;**62:**127–41.
11. Helliwell P, Marchesoni A, Peters M, Barker M, Wright V. A re-evaluation of the osteoarticular manifestations of psoriasis. *Br J Rheumatol* 1991;**30:**339–45.
12. Kirwan JR, Reedback JS. Stanford Health Assessment Questionnaire modified to assess disability in British patients with rheumatoid arthritis. *Br J Rheumatol* 1986;**25:**206–9.
13. Fries JF, Spitz PW, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. *Arthritis Rheum* 1980;**23:**137–45.
14. Fredericksson T, Petterson U. Severe psoriasis—oral therapy with a new retinoid. *Dermatologica* 1978;**157:**238–42.
15. Benhamou CL, Chamot MA, Khan MF. Synovitis-acne-pustulosis-hyperostosis-osteomyelitis syndrome (SAPHO)—a new syndrome among the spondyloarthropathies? *Clin Exp Rheumatol* 1988;**6:**109–12.
16. Camp RDR. Psoriasis. In: Barton JL *et al.* eds. *Textbook of dermatology*, 5th edn. Oxford: Blackwell;1992:1359–1458.
17. Roberts MET, Wright V, Hill AGS. Psoriatic arthritis: follow-up study. *Ann Rheum Dis* 1976;**35:**206–12.
18. Potter EM, McEwan C. Psoriatic arthritis: clinical features with particular reference to distal interphalangeal joint involvement. *Br J Rheumatol* 1992;**31:**646–7.
19. Wright V. Psoriasis and arthritis. *Ann Rheum Dis* 1956;**15:**348–56.
20. Wright V. Rheumatism and psoriasis. A revaluation. *Am J Med* 1959;**27:**454–62.
21. Wright V. Psoriatic arthritis: a comparative study of rheumatoid arthritis and arthritis associated with psoriasis. *Ann Rheum Dis* 1961;**20:**123–31.
22. Wright V, Moll JMH. Psoriatic arthritis. *Bull Rheum Dis* 1971;**21:**627–32.
23. Avila R, Pugh DG, Slocomb CH, Winklemann RK. Psoriatic arthritis: a roentgenographic study. *Radiology*1960;**75:**691–701.
24. Moll JMH, Wright V. Psoriatic arthritis. *Semin Arthritis Rheum* 1973;**3:**55–78.
25. Moll JMH. The clinical spectrum of psoriatic arthritis. *Clin Orthop Rel Res* 1979;**143:**66–75.
26. Little H, Harvie JN, Lester RS. Psoriatic arthritis in severe psoriasis. *Can Med Ass J* 1975;**112:**317–19.

27. LLeonard DG, O'Duffy JD, Rogers RS. Prospective aanalysis of psoriatic arthritis in patients hospitalized fdfor psoriasis. *Mayo Clin Proc* 1978;**53:**511618.
28. MMolin J. Psoriatic arthritis. *Ann Clin Res* 1978;**8:**305–11.
29. SScarpa R, Oriente P, Pulima A *et al.* Psoriatic arthritis iin psoriatic patients. *Br J Rheumatol* 1984;**23:**246–50.
30. MMoll JMH. Psoriatic arthritis. *Br J Rheumatol* 1984;**23:**241–5.
31. MMcCormack GD, Barth W. Classification and diagnnosis of psoriatic arthritis. In: *Psoriatic arthritis* (Gerbber LH, Espinoza LR, eds.) New York: Grune and SStratton; 1985:59–82.
32. VVeale D, Rogers S, Fitzgerald O. Classification of clinicacal subsets in psoriatic arthritis. *Br J Rheumatol* 1994;**33:**133–8.
33. GGladman DG, Anhorn KAB, Schachter RK, Mervart HH. HLA antigens in psoriatic arthritis. *J Rheumatol* 1986;**13:**586.
34. Kammer GM, Soter NA, Gibson DJ, Schur PH. Psoriatic arthritis: A clinical, immunologic and HLA study of 100 patients. *Semin Arthritis Rheum* 1979;**9:**75–97.
35. Barraclough D, Russell AS, Percy JS. Psoriatic spondylitis: a clinical, radiological and scintiscan survey. *J Rheumatol* 1977;**4:**282.
36. Torre Alonso JC, Rodriguez Perez A, Arribas Castrillo JM *et al.* Psoriatic arthritis (PA). A clinical, immunological and radiological study of 180 patients. *Br J Rheumatol* 1991;**31:**245–50.
37. Gladman DD. Psoriatic arthritis: recent advances in pathogenesis and treatment. *Rheum Dis Clin North Am* 1992;**18:**247–56.
38. McHugh NJ, Laurent MR, Treadwell BLJ, Tweed JM, Dagger J. Psoriatic arthritis: clinical subgroups and histocompatibility antigens. *Ann Rheum Dis* 1987;**46:**186–8.

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# EXPRESSION OF THE CUTANEOUS LYMPHOCYTE ANTIGEN AND ITS COUNTER-RECEPTOR E-SELECTIN IN THE SKIN AND JOINTS OF PATIENTS WITH PSORIATIC ARTHRITIS

**S. M. JONES, J. DIXEY,* N. D. HALL† and N. J. McHUGH**

*Royal National Hospital for Rheumatic Diseases, *Bath Institute for Rheumatic Diseases and †School of Pharmacy and Pharmacology, University of Bath, Bath*

## SUMMARY

We have investigated whether the skin-homing T lymphocytes identified by the cutaneous lymphocyte antigen (CLA) are increased in the synovial membrane of patients with psoriatic arthritis. Twenty-six synovial samples (13 psoriatic arthritis, seven rheumatoid arthritis, six osteoarthritis) were obtained from involved knees. Lesional skin biopsies were taken from nine of the patients with psoriatic arthritis and six patients with psoriasis alone. All samples were single- and dual-stained for CLA and CD3 (to identify T lymphocytes) using HECA-452 (anti-CLA) and anti-CD3 monoclonal antibodies. E-selectin expression was also determined. The percentage of dual-stained lymphocytes was significantly greater in psoriatic skin than in synovium ($P < 0.001$) and similar between psoriatic and rheumatoid synovium. There was no significant difference in the percentages of CLA-positive cells in psoriatic skin in patients with psoriatic arthritis compared with psoriasis alone. The intensity of endothelial E-selectin expression was significantly greater in skin psoriasis than in synovium ($P < 2 \times 10^{-5}$), and rheumatoid synovium had significantly greater expression than psoriatic synovium ($P < 0.05$). However, there was no significant correlation between E-selectin expression and the percentages of CLA-positive lymphocytes. This study provides further evidence that the CLA antigen is enriched on skin-homing lymphocytes. Conversely, the link between skin and joint inflammation in psoriatic arthritis does not seem to be explained by increased trafficking of CLA T cells to psoriatic synovium.

KEY WORDS: Psoriatic arthritis, Synovium, T cell, Cutaneous lymphocyte antigen (CLA), E-selectin.

PSORIASIS is an inflammatory and proliferative skin disorder with a prevalence of 1.5–3%. Approximately 20% of patients with psoriasis develop a characteristic form of arthritis that has several patterns [1–5]. Some individuals present with joint symptoms first, but in the majority, skin psoriasis presents first. About one-third of patients have simultaneous exacerbations of their skin and joint disease [6], and there is a topographic relationship between nail and distal interphalangeal joint disease [4, 7]. Gerber and Espinoza [8] postulated that 'noxious substances' may traffic between the sites, linking their involvement. Although the inflammatory processes which link skin, nail and joint disease remain elusive, an immune-mediated pathology is implicated.

Immunopathogenic mechanisms involving T lymphocytes in psoriasis and arthritis appear similar. Both the skin and synovium are infiltrated with activated T lymphocytes [9, 10], with a preponderance of CD4R1O+ cells, known to migrate preferentially to peripheral tissues [10]. There are known associations with major histocompatibility haplotypes [11, 12]. Both psoriasis and arthritis increase in severity with the depletion of T-helper lymphocytes secondary to HIV infection [13, 14], and both improve in response to immunotherapy such as cyclosporin A.

The skin is a functionally unique immune site with apparently a specific homing mechanism for T cells. The cutaneous lymphocyte antigen (CLA), defined by the monoclonal antibody HECA-452, identifies a population of skin-homing memory T cells [15]. The receptor for CLA on dermal endothelium is the inducible cell adhesion molecule E-selectin [16], a protein which also acts to tether neutrophils during their initial rolling interaction with the blood vessel wall at the onset of an inflammatory response [17, 18]. It has been proposed that E-selectin on venules at sites of acute inflammation supports neutrophil recruitment, whereas in sites of chronic inflammation in the skin it mediates accumulation of CLA-positive T cells [16].

The principal aim of the current study was to determine whether skin and joint disease in psoriatic arthritis may be linked through the inappropriate expression of CLA molecules, E-selectin or both. We have therefore investigated the percentages and distribution of skin-homing (CLA-positive) T lymphocytes and their counter-receptor E-selectin in the skin, synovium and peripheral blood of patients with psoriatic arthritis and appropriate controls.

## MATERIALS AND METHODS

The study was approved by the Bath and South West Ethical Committee. Written consent was obtained for biopsies.

### *Patients*

Thirteen patients with psoriatic arthritis and synovitis of a knee were recruited from a psoriatic arthritis clinic. Clinical information including the age, sex, duration of psoriasis and arthritis, subgroup of joint disease, presence of erosions, degree of knee synovitis, skin severity, periodicity of skin and joint

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Correspondence to: S. M. Jones, Royal National Hospital for Rheumatic Diseases, Upper Borough Walls, Bath BA1 1RL.

disease, and the presence of nail disease was recorded. All patients had active psoriasis and were seronegative for rheumatoid factor.

Controls included samples from seven patients with seropositive rheumatoid arthritis (RA) defined by the American College of Rheumatology [19], six patients with osteoarthritis and six patients with psoriasis alone. No patient or control had received an intra-articular steroid injection within 3 months of obtaining synovial samples.

*Immunohistochemistry*

*Sample collection. (1) Synovium:* Biopsies were taken from knee joints by a standard blind needle biopsy technique using a Polley's needle after local anaesthesia. At least six samples of synovial membrane were obtained from different regions of the suprapatellar pouch. Paraffin sections were obtained for descriptive histology. Samples from two of the patients with RA and three of the six patients with osteoarthritis were obtained at the time of arthroscopy or joint replacement.

*(2) Skin*: Elliptical skin samples were obtained from nine patients with psoriatic arthritis, eight of whom had concurrent synovial biopsies, and six patients with psoriasis alone, recruited from a dermatology clinic. A musculoskeletal history and joint examination were performed to confirm the absence of arthritis in the latter patients. Biopsies were taken from lesional edges of the most active accessible plaques. In one patient, the skin biopsy was taken from a plaque directly on the involved knee.

Further control tissue included three samples of normal skin from healthy volunteers, one sample of lesional skin from a patient with severe eczema, and a sample of normal tonsil.

*Preparation of sections*. Tissue sections of skin and synovium were mounted on cork with 5% polyvinyl alcohol (PVA), snap frozen in liquid nitrogen and stored at −70°C. The cork was mounted onto a metal chuck with PVA and 8 μm sections were cut on a cryostat at −25°C. Sections were mounted serially on 4-well glass slides, air-dried for 1 h and fixed in acetone at room temperature for 10 min, wrapped in tin-foil and stored at −20°C prior to use. Histology was checked every 10 sections using a rapid staining technique (Diffquick). Synovial specimens without clearly defined synovial lining cells, and skin specimens without identifiable epidermis and dermis, were discarded.

*Materials*. The antibodies and other reagents used are listed in Table I. The monoclonal antibody HECA-452 was provided by Dr Louis Picker, University of Texas, USA.

*Single-staining for CD3 and CLA*. CD3 populations were quantified using anti-CD3 supernatant (undiluted) or control mouse IgG (dilution 1 in 500) and alkaline phosphatase/monoclonal anti-alkaline phosphatase (APAAP) complexes using a standard method described by the manufacturer (Dakopatts).

Sections were stained for CLA using HECA-452 (rat IgM) and a standard biotin/streptavidin–alkaline phosphatase technique: (1) blocking step for 20 min with human AB serum in 5% solution with Tris-buffered saline (TBS); (2) 1 h incubation with HECA-452 monoclonal antibody (rat IgM) at 1/30 dilution or control rat IgM (1/100 dilution); (3) 30 min incubation with biotinylated species-specific anti-rat immunoglobulins at 1/50 dilution; (4) 30 min incubation with streptavidin–alkaline phosphatase at 1/50 dilution; (5) Fast red/substrate for 15–20 min at room temperature. All reagents were diluted in TBS and 100 μl of diluent used for each section. Each stage was followed by washing for 1–2 min in TBS. Finally, the sections were lightly counterstained with haematoxylin and mounted.

The HECA-452 monoclonal antibody is not T-cell specific, but also identifies related E-selectin ligands on high endothelial venules (HEVs), neutrophils and monocytes. Therefore, double fluorescence staining was used to estimate the percentage of CLA-positive T lymphocytes.

TABLE I
Antibodies, reagents and their sources

| Antibody/conjugates | Reactivity | Isotype | Source |
|---|---|---|---|
| Immunohistology | | | |
| HECA-452 | CLA | Rat IgM | L. Picker |
| Anti-CD3 | CD3 | Mouse IgG | Own laboratory |
| Rat IgM (control) | Undefined | Myeloma rat IgM | Serotec |
| Mouse IgG1 (control) | Undefined | Mouse IgG1 | Sigma |
| Anti-rat IgGs | Rat Igs—all subclasses | Rabbit | Dakopatts |
| Anti-mouse IgG | Mouse Igs—all subclasses | Polyclonal | Dakopatts |
| Anti-mouse IgG–TRITC conjugate | Mouse IgGs | Polyclonal | Sigma |
| FITC-conjugated streptavidin | NA | NA | Dakopatts |
| ALP-conjugated streptavidin | NA | NA | Dakopatts |
| Anti-E selectin (clone H4/18) | E-selectin | Mouse IgG1 | R and D Systems |
| Anti-CD34 | CD34 | Mouse IgG1 | Dakopatts |
| APAAP | Alkaline phosphatase | Mouse IgG1 | Dakopatts |
| Flow cytometry | | | |
| FITC–HECA-452 | CLA | Rat IgM | L. Picker |
| FITC control | Undefined | Rat IgM | L. Picker |
| PE-conjugated anti-CD3 | CD3 | Mouse IgG | Dakopatts |

*Fluorescence double-staining*. Sections were double-stained for CLA and CD3 using HECA-452 and anti-CD3 supernatant and fluorescein isothiocyanate (FITC) and tetramethylrhodamine isothiocyanate (TRITC) conjugates, respectively, and appropriate non-reactive control monoclonal antibodies. Each serial 4-well slide had a control section, single-stained sections for CLA and CD3, and a double-stained section. The incubation steps for double-staining were: (1) 20 min blocking step with human AB serum in 5% solution with phosphate-buffered saline (PBS); (2) 45 min incubations with anti-CD3 supernatant (undiluted) and goat TRITC anti-mouse IgG (1 in 50); (3) 20 min blocking step with 5% normal mouse serum (NMS); (4) HECA-452 monoclonal antibody (1/30 dilution); (5) 45 min incubation with rabbit biotinylated species-specific anti-rat immunoglobulins (1/50); (6) FITC–streptavidin (1/50). All antibodies were diluted in PBS and each stage was followed by washing for 1–2 min with PBS. The sections were mounted using 1,4-diazabicyclo(2,2,2)octane (DABCO) as an interface.

Three psoriatic synovial sections were similarly double-stained for macrophages using anti-CD68 instead of anti-CD3.

Sections were stained in duplicate or triplicate, blinded to the diagnosis and scored by two investigators (SJ and JD). The numbers of single- and double-stained T lymphocytes were assessed in the dermis of the skin and sublining layer of the synovium. Sequential fields were studied using an eyepiece orientated along the dermo-epidermal junction or synovial lining layer. A section was only scored if the singly stained section was of equivalent intensity to the dual-stained section. Inter-observer variability was within 10%.

*Determination and quantitation of E-selectin expression*. The anti-E-selectin monoclonal antibody was used followed by the APAAP complex, according to the protocol described by the manufacturers (Dakopatts), followed by haematoxylin counterstaining. Endothelial morphology was confirmed in longitudinally cut vessels by the endothelial cell marker anti-CD34. Anti-E selectin was used at a dilution of 1/200, anti-CD34 and APAAP at 1/50. Vessels in the dermis of the skin and synovial sublining were scored in sequential fields. The number of vessels, the proportion of E-selectin-positive vessels and the intensity of staining were determined on an arbitrary scale as follows: 0 = no staining detected; 1 = minimal staining; 2 = moderate staining; 3 = strong staining. The mean intensity was computed for each section. The density of the surrounding inflammatory infiltrate was also determined using the following scale: 0 = no inflammatory infiltrate; 1 = small inflammatory infiltrate; 2 = moderate inflammatory infiltrate; 3 = dense inflammatory infiltrate.

*Flow cytometry*

*Sample collection*. Ten millilitres of venous blood were taken from 12 patients with psoriatic arthritis, six with RA and six normal controls. All the psoriatic arthritis and RA patients had clinical evidence of active synovitis. Three of the psoriatic arthritis patients were included in the immunohistological study (Table II, patients 3, 4 and 7).

*Materials*. The reagents used are listed in Table I. The FITC-conjugated HECA-452 monoclonal antibody and a control FITC-conjugated rat IgM with unspecified reactivity were donated by Dr Picker and used undiluted.

*Methods*. Mononuclear cells (MNC) were separated from 10 ml of heparinized whole blood using a standard lymphoprep gradient. Briefly, 10 ml of heparinized blood were taken from each patient. The separated MNCs were washed with medium, counted and resuspended in RPMI and 10% fetal calf serum, and pre-incubated with 50 $\mu$l of undiluted normal

TABLE II
Clinical characteristics of psoriatic arthritis patients

| Patient | Age (yr) | Sex | Duration of arthritis (yr) | Duration of psoriasis (yr) | Subgroup | Erosions | Knee synovitis | Historical skin severity | PASI score* (0–72) | Nail disease | Nail score† (0–40) | Simultaneous skin and joint exacerbations |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 59 | F | 27 | 28 | Mutilans | y | 2 | 3 | 4.2 | n | 0 | n |
| 2 | 62 | F | 18 | 10 | Polyarthritis | y | 3 | 3 | 4.8 | n | 0 | n |
| 3 | 53 | M | 24 | 36 | Polyarthritis | y | 1 | 2 | 4.2 | y | 4 | y |
| 4 | 40 | M | 6 | 16 | Polyarthritis | y | 2 | 2 | 4.4 | y | 17 | n |
| 5 | 38 | M | 7 | 8 | Oligoarthritis | n | 1 | 2 | 2.1 | y | 6 | n |
| 6 | 20 | F | 6 | 8 | Oligoarthritis | n | 3 | 1 | 2.7 | y | 7 | y |
| 7 | 30 | M | 26 | 9 | Polyarthritis | n | 1 | 3 | 4.1 | y | 0 | y |
| 8 | 62 | M | 22 | 22 | Polyarthritis | y | 3 | 3 | 1.2 | y | 5 | n |
| 9 | 42 | F | 7 | 20 | Oligoarthritis | n | 1 | 1 | 0.6 | y | 0 | n |
| 10 | 40 | M | 12 | 12 | Oligoarthritis | n | 2 | 2 | 2.1 | n | 0 | n |
| 11 | 48 | M | 20 | 33 | Polyarthritis | y | 2 | 2 | 2.4 | y | 18 | n |
| 12 | 46 | F | 15 | 30 | Polyarthritis | y | 2 | 2 | 0.5 | y | 7 | y |
| 13 | 34 | F | 6 | < 1 | Polyarthritis | y | 3 | Trivial | 0 | y | 3 | n |

Patients 3 and 7 had insufficient synovial lymphocytes for quantitative assessment.
Paired skin samples were available on patients 1–8.
Historical skin severity and knee synovitis are graded on a three-point scale: 1 = mild; 2 = moderate; 3 = severe.
*Reference [28].
†Reference [4].

human serum. A total of $5 \times 10^5$ cells were used per test. The following reagents were added: (1) anti-CD3, (2) phycoerythrin (PE)-conjugated anti-mouse immunoglobulins (1/50) and (3) FITC-conjugated HECA-452 monoclonal antibody (undiluted) with appropriate controls minus one or more reagents. After 30 min incubation, the cells were resuspended in PBS containing 1% paraformaldehyde.

Flow cytometry was performed using a Becton-Dickinson FACStar Plus with an air-cooled argon laser and Consort 32 computer. Gating was performed by setting the threshold with reference to the relevant negative control. The percentages of CLA-positive circulating T lymphocytes in the peripheral blood of patients with psoriatic arthritis, RA and normal controls were determined.

*Data analysis*

Data were analysed using a Hewlett Packard personal computer with software packages including Microsoft EXCEL and STATMOST. Normality testing was performed prior to analysis. Duncan's test for multiple comparisons was used for the various patient groups. The Mann–Whitney *U*-test was used to compare all the psoriatic skin versus the synovial samples. The Wilcoxon signed rank test was used for paired psoriatic skin and synovial data. Spearman's rank coefficient was used for correlation analysis.

## RESULTS

*Clinical characteristics*

The patients represented a spectrum of disease severity for both joint and skin disease (Table II). There were six females and seven males, mean age 44 (range 20–62 yr) and mean duration of arthritis 15 yr (range 6–27) and psoriasis 18 yr (range 0–36). One patient (patient 13) had trivial psoriasis only that at the time of synovial biopsy did not reach the criteria for a PASI score. The immunohistological data were assessed in relation to clinical parameters.

*Immunohistology*

*T-lymphocyte populations.* The distribution of T lymphocytes in each sample was quantified prior to double-staining (Table III). Eight synovial samples (six osteoarthritis, two psoriatic arthritis) did not have sufficient lymphocytic infiltration to determine accurately the percentages of CLA-positive T cells. The two psoriatic arthritis patients had only mild synovitis at the time of biopsy. For the six osteoarthritis patients, only isolated lymphocytes were present, with an occasional double-stained cell. Apart from the osteoarthritis group, the mean numbers of T cells per field (T-cell density) were similar in the other four patient groups. There was a weak negative correlation between the T-cell density in synovium and the duration of arthritis, but this was not significant. There was also a weak positive correlation between the degree of synovitis clinically in psoriatic arthritis and the T-cell density, but this was not statistically significant.

*Immunohistological distribution of the CLA antigen.* The CLA antigen was present on many cell types within the synovium, including T cells, vascular endothelium, neutrophils and macrophages. Its presence on macrophages was also confirmed by double-labelling with an anti-CD68 monoclonal antibody. In the skin, CLA-positive lymphocytes were observed in all lymphocytic areas, both in perivascular lymphoid aggregates around superficial dermal vessels, immediately below the stratum basale and in the more diffuse cellular infiltrate. Other skin cell types also stained for

TABLE III
T-lymphocyte densities and percentages of CLA-positive cells in psoriatic arthritis, rheumatoid arthritis synovium and psoriatic skin

| Sample number | Number of T cells per HPF (×40) mean (range) | Number of T cells counted | % CLA-positive T cells |
|---|---|---|---|
| Psoriatic synovium* | | | |
| 1 | 18 (11–32) | 107 | 11.2 |
| 2 | 20 (13–26) | 101 | 4 |
| 3 | < 1 | ND | ND |
| 4 | 92 (32–231) | 369 | 3.8 |
| 5 | 10 (8–11) | 39 | 15 |
| 6 | 38 (16–55) | 269 | 3.3 |
| 7 | 8 (1–39) | 631 | 7.1 |
| 8 | 4 (1–13) | 159 | 34 |
| 9 | < 1 | ND | ND |
| 10 | 25 (12–40) | 253 | 7.5 |
| 11 | 11 (1–53) | 310 | 4.2 |
| 12 | 11 (3–21) | 157 | 5.7 |
| 13 | 9 (5–13) | 53 | 11 |
| Mean (S.D.) | 22 (25) | 307 (173) | 9.7 (8.9) |
| RA synovium | | | |
| 1 (surgical) | 1 (0–45) | 362 | 14 |
| 2 | 44 (33–52) | 261 | 2.7 |
| 3 | 16 (9–25) | 197 | 10 |
| 4 | 7 (3–11) | 51 | 3.9 |
| 5 | 41 (19–67) | 285 | 4.9 |
| 6 (surgical) | 27 (11–65) | 348 | 14.4 |
| 7 | 30 (21–38) | 180 | 2.2 |
| Mean (S.D.) | 24 (16.4) | 241 (108) | 7.4 (5.3) |
| Psoriasis in psoriatic arthritis* | | | |
| 1 | 10 (5–14) | 52 | 51.9 |
| 2 | 11 (6–16) | 56 | 46.4 |
| 3 | 17 (7–34) | 121 | 41.3 |
| 4 | 21 (13–26) | 170 | 50.6 |
| 5 | 23 (3–58) | 132 | 56.1 |
| 6 | 35 (19–66) | 283 | 57.6 |
| 7 | 12 (6–24) | 167 | 32.3 |
| 8 | 25 (11–40) | 197 | 48.2 |
| 9 | 35 (13–47) | 212 | 42.9 |
| Mean (S.D.) | 19 (9.6) | 147 (74) | 47.5 (7.9) |
| Psoriasis | | | |
| 1 | 26 (6–15) | 104 | 43.3 |
| 2 | 36 (24–39) | 254 | 57.8 |
| 3 | 11 (8–20) | 100 | 38 |
| 4 | 20 (9–28) | 256 | 39.5 |
| 5 | 6 (2–11) | 51 | 60.8 |
| 6 | 24 (17–39) | 166 | 75.3 |
| Mean (S.D.) | 21 (10.1) | 155 (85.5) | 52.4 (14.7) |

ND, not done.
*Psoriatic synovial samples 1–8 are paired with psoriatic arthritis skin samples 1–8.

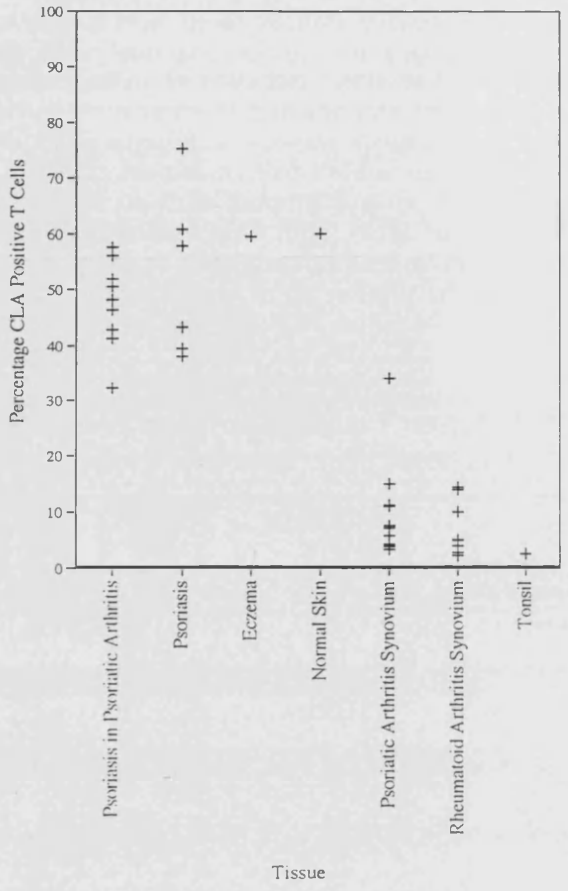


FIG. 1.—Percentages of T lymphocytes that are CLA positive in psoriasis with and without arthritis, eczema, normal skin, psoriatic arthritis synovium, rheumatoid arthritis synovium and tonsil.

HECA-452 including macrophages, polymorphonuclear leucocytes, vascular endothelial cells and Langerhans cells.

*CLA/CD3 double-staining*. The percentages of CLA/CD3 double-stained lymphocytes in patient groups and control tissue are shown in Table III and Fig. 1. Representative results of fluorescence double-staining of CD3 and CLA for psoriatic skin and synovium are shown in Fig. 2a–d. There was a significant correlation between the density of the inflammatory infiltrate and the percentages of CLA-positive T cells ($P < 0.05$).

The following comparisons between disease groups were made: (a) all skin ($N = 19$) and all synovial samples ($N = 18$); (b) psoriasis ($N = 15$) and psoriatic arthritis synovium ($N = 11$); (c) psoriatic arthritis synovium ($N = 9$) and RA synovium ($N = 7$); (d) paired psoriatic arthritis synovial membrane and skin samples ($N = 7$); (e) psoriasis in patients with arthritis ($N = 8$) and those without arthritis ($N = 6$).

The percentages of lymphocytes double-stained for CLA and CD3 were significantly greater in (a) skin than synovium ($P < 10^{-6}$) and (b) psoriasis than psoriatic arthritis synovium ($P = 0.01$). For paired skin and synovial samples from psoriatic arthritis patients, the percentages of double-stained lymphocytes were also significantly greater in skin than synovium ($P < 0.02$). In one paired sample of psoriatic skin and synovium (patient 8), the percentage expression was 48.5 and 34%, respectively.

There were no significant differences between the percentages of double-stained lymphocytes in psoriatic arthritis synovium compared with RA synovium. In skin psoriasis, there were no significant differences in the percentages of CLA-positive lymphocytes in patients who had arthritis compared with those with psoriasis alone. The percentages in the three samples of normal skin and from one sample of eczematous skin were similar (all 60%), but much less in tonsil (2.5%).

There were no significant associations between any clinical parameter and the percentages of double-stained lymphocytes in synovial tissue. There were no significant associations between the degree of synovitis clinically and the percentage of double-stained lymphocytes. In particular, there were no significant differences between the percentages of double-stained lymphocytes in the four patients who had coincident exacerbations of their skin and joint disease, and those in whom there was no apparent temporal association. The patient with the greatest percentage of double-stained lymphocytes in synovium (34%) did have simultaneous exacerbations of his skin and joint disease.

*E-selectin expression*. The mean number of blood vessels per field, the percentage of positively stained vessels, the E-selectin intensity and the density of the perivascular infiltrate are shown in Table IV. Comparisons between the percentages of positive vessels, E-selectin intensities, numbers of vessels and perivascular infiltrates were made in the following groups: (a) all skin ($N = 18$) and all synovial samples ($N = 16$); (b) all psoriasis ($N = 15$) and psoriatic arthritis synovium ($N = 10$); (c) psoriatic arthritis synovium ($N = 10$) and RA synovium ($N = 6$); (d) paired psoriatic arthritis synovial membrane and skin samples ($N = 6$); (e) psoriasis in patients with arthritis ($N = 8$) and those without arthritis ($N = 6$).

The results for the disease group comparisons for the intensity of E-selectin expression were as follows: (a) E-selectin expression was significantly greater in skin than synovium ($P < 2 \times 10^{-6}$) and (b) in skin psoriasis compared with psoriatic synovium ($P < 2 \times 10^{-5}$); (c) E-selectin expression was significantly greater in RA synovium compared with psoriatic arthritis synovium ($P < 0.05$); (d) in paired skin and synovial samples from patients with psoriatic arthritis, E-selectin expression was significantly greater in skin than synovium ($P < 0.018$); (e) there was no significant difference in E-selectin expression in the skin of patients with arthritis compared with those without arthritis. When the numbers of positive vessels were used instead of E-selectin intensity, the results of these comparisons were similar. In 3/10 psoriatic arthritis synovial samples and 1/7 RA synovial samples, no E-selectin expression was seen. Minute quantities only of E-selectin were detected in osteoarthritis synovial membrane. In skin, E-selectin was expressed in all

samples throughout the dermal vessels, including the deep dermal vasculature, and was present in all samples. E-selectin expression in skin and synovium is shown in Fig. 3.

The numbers of vessels per field were significantly greater in synovium than all the skin samples, including the three samples of eczema and normal skin ($P < 0.03$), and the difference remained significant

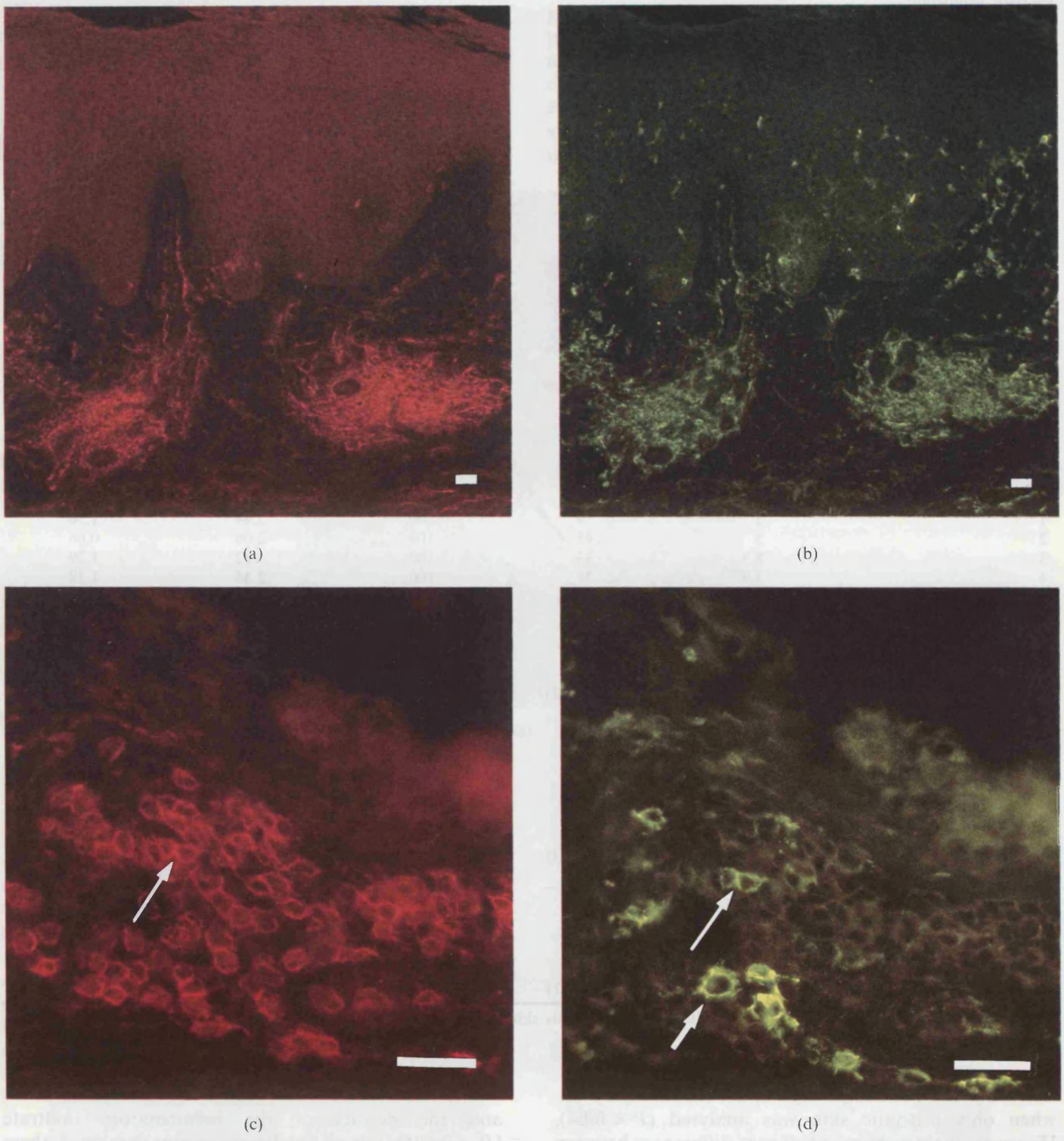

FIG. 2.—Photomicrographs of fluorescence dual staining of psoriatic skin and psoriatic arthritis synovium. (a) TRITC anti-CD3-labelled lymphocytes in skin psoriasis (stained red; green filter) (original magnification ×20); (b) FITC HECA-452-labelled cells in psoriasis (original magnification ×20). The majority of T lymphocytes in the aggregate are CLA positive. (c) TRITC anti-CD3-labelled lymphocytes in psoriatic arthritis synovium (stained red; green filter) (original magnification ×40); (d) FITC HECA-452-labelled cells in psoriatic arthritis synovium (stained green; red filter) (original magnification ×40). Almost all of the lymphocytes are CLA negative. A rare pair of dual-stained lymphocytes are shown (long arrows). A non-lymphocytic cell labelled with the HECA-452 monoclonal antibody is also shown (short arrow). The bar represents 100 μm.

TABLE IV
Number of vessels per field, expression of E-selectin and density of perivascular infiltrate in psoriatic arthritis, rheumatoid arthritis synovium and all skin samples

| Sample number | Number of vessels per HPF (×20) (mean) | Number of vessels counted | Percentage of positive vessels | E-selectin intensity (mean) | Density of perivascular infiltrate (mean) |
|---|---|---|---|---|---|
| Psoriatic synovium* | | | | | |
| 1 | 10 | 30 | 33 | 1 | 1.93 |
| 2 | 4.3 | 18 | 50 | 0.65 | 1.35 |
| 3 | ND | ND | ND | ND | ND |
| 4 | 4.3 | 13 | 0 | 0 | 0.85 |
| 5 | ND | ND | ND | ND | ND |
| 6 | 4.2 | 25 | 16 | 0.2 | 0.76 |
| 7 | 7.1 | 50 | 0 | 0 | 1.2 |
| 8 | 8.75 | 70 | 13 | 0.65 | 1.35 |
| 9 | ND | ND | ND | ND | ND |
| 10 | 6.5 | 65 | 35 | 0.54 | 1.37 |
| 11 | 4.5 | 18 | 22 | 0.22 | 1.22 |
| 12 | 10 | 10 | 0 | 0 | 0.2 |
| 13 | 10 | 10 | 20 | 0.2 | 1.3 |
| Mean (S.D.) | 7 (2.6) | 30.9 (22.7) | 18.9 (16.8) | 0.35 (0.34) | 1.16 (0.46) |
| Rheumatoid arthritis synovium | | | | | |
| 1 (surgical) | ND | ND | ND | ND | ND |
| 2 | 5 | 10 | 50 | 0.7 | 0.7 |
| 3 | 5.5 | 11 | 9 | 0.09 | 0.36 |
| 4 | ND | ND | ND | ND | ND |
| 5 | 15.3 | 92 | 64 | 1.38 | 1.63 |
| 6 (surgical) | 5.9 | 142 | 48 | 0.77 | 0.77 |
| 7 | 2.3 | 7 | 0 | 0 | 2.86 |
| 8 | 6.9 | 104 | 62 | 1.31 | 1.14 |
| Mean (S.D.) | 6.8 (4.4) | 61 (59) | 38.8 (27.5) | 0.71 (0.58) | 1.24 (0.9) |
| Psoriasis in psoriatic arthritis* | | | | | |
| 1 | 3 | 9 | 100 | 2.44 | 1.56 |
| 2 | 5 | 45 | 100 | 2.06 | 0.66 |
| 3 | 8.3 | 33 | 100 | 1.82 | 1.39 |
| 4 | 3.9 | 27 | 100 | 2.44 | 1.19 |
| 5 | 6 | 30 | 100 | 2.67 | 1.8 |
| 6 | 6.6 | 39 | 87 | 1.66 | 1.27 |
| 7 | 4.8 | 43 | 100 | 1.95 | 1.02 |
| 8 | 11.3 | 102 | 84 | 1.95 | 1.22 |
| 9 | 5 | 15 | 100 | 2.87 | 2.13 |
| Mean (S.D.) | 6 (2.5) | 40.3 (27.7) | 96.8 (6.4) | 2.21 (0.41) | 1.36 (0.43) |
| Psoriasis | | | | | |
| 1 | 2.5 | 10 | 100 | 1.6 | 1.7 |
| 2 | 2.8 | 14 | 100 | 1.29 | 1.86 |
| 3 | 1.5 | 12 | 100 | 2.5 | 1.25 |
| 4 | 4 | 16 | 94 | 1.81 | 1.44 |
| 5 | 4.2 | 21 | 100 | 2.48 | 1.29 |
| 6 | 3.7 | 46 | 100 | 1.6 | 1.33 |
| Mean (S.D.) | 3.7 (1.0) | 28.8 (13.3) | 99 (2.4) | 2.09 (0.5) | 1.53 (0.25) |
| Eczema | | | | | |
| 1 | 5.4 | 27 | 89 | 2.3 | 1.78 |
| Normal | | | | | |
| 1 | 3.7 | 11 | 18 | 0.18 | 0.73 |
| 2 | 2 | 10 | 80 | 0.9 | 0.6 |
| Mean (S.D.) | 2.9 (1.2) | 10.5 (0.71) | 49 (43.8) | 0.54 (0.51) | 0.67 (0.09) |

*Psoriatic synovial samples 1–8 are paired with psoriatic arthritis skin samples 1–8.
All samples correspond to those in Table III.

when only psoriatic skin was analysed ($P < 0.04$). However, there were no significant differences between the numbers of vessels per field between any of the remaining disease groups.

There were no significant differences in the density of the perivascular infiltrates between the patient groups. For psoriatic arthritis synovium, there was a significant correlation between E-selectin expression and the density of the inflammatory infiltrate ($P < 0.005$). For all the disease groups combined, there was a weak positive correlation between E-selectin expression and the density of the inflammatory infiltrate, but this was not significant. There were no significant correlations between E-selectin intensity and any clinical parameter or the percentages of CLA-positive T cells.

*CLA-positive T cells in peripheral blood.* Flow cytometry results for T lymphocytes double-stained for CD3 and CLA are shown in Fig. 4. Patients with RA had slightly greater percentages of double-stained cells (median 4.8, range 2.6–8.4%) than those with psoriatic arthritis (median 2.9, range 1.4–5.8%) and four normal control patients (median 2.0, range 1.1–5.7). The differences between the disease and normal control groups were not significant.

## DISCUSSION

Patients with psoriatic arthritis provide a unique opportunity for studying tissue-specific homing mechanisms that contribute to chronic inflammation. We have obtained paired samples of chronically inflamed skin and synovium from such patients, spanning all the patterns and severities of peripheral joint disease with the common features of knee synovitis and active skin disease. Our major finding is that there is a significantly greater percentage of CLA-positive lymphocytes in psoriatic skin compared with synovium in psoriatic arthritis, and that this difference is independent of the clinical characteristics. The data confirm previous evidence that the CLA molecule is enriched only on skin-homing T lymphocytes [15] and are similar to the results reported in another recent study of psoriatic

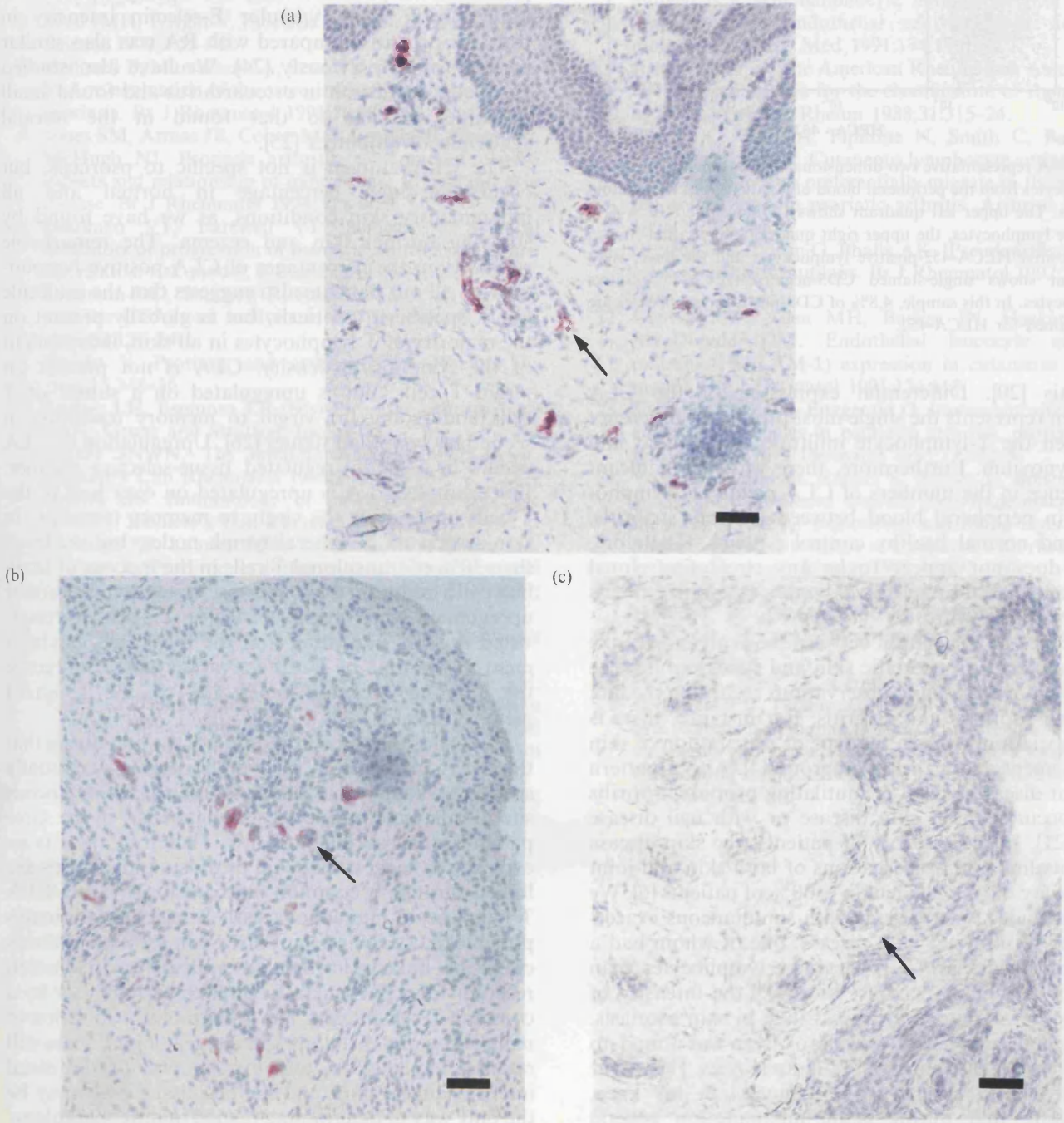


FIG. 3.—Differing intensities of E-selectin expression on vascular endothelium in (a) psoriasis, (b) rheumatoid arthritis synovium and (c) psoriatic arthritis synovium. A typical vessel in each section is indicated by the arrows. The bar represents 100 $\mu$m.

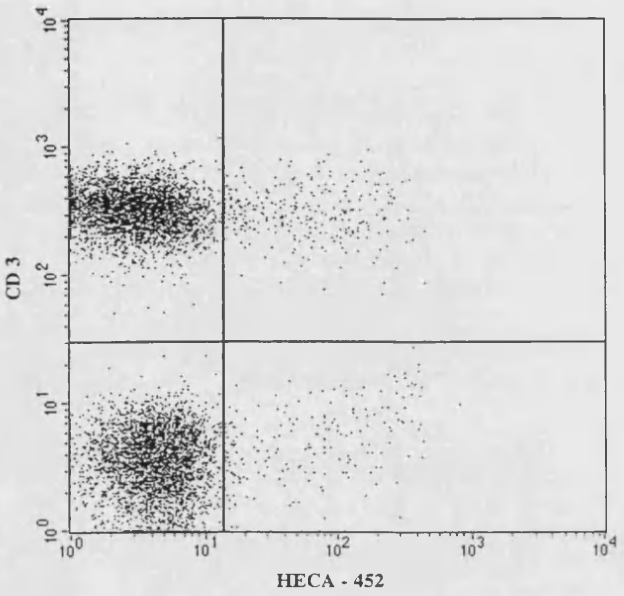


FIG. 4.—A representative two-dimensional flow cytometric profile of lymphocytes from the peripheral blood of a patient with rheumatoid arthritis. The upper left quadrant shows CD3-positive/HECA-452-negative lymphocytes, the upper right quadrant shows dual-stained CD3-positive/HECA-452-positive lymphocytes and the lower right quadrant shows single-stained CD3-negative/HECA-452-positive lymphocytes. In this sample, 4.8% of CD3-positive lymphocytes are dual-stained for HECA-452.

arthritis [20]. Differential expression of the CLA antigen represents the single most prominent difference between the T-lymphocyte infiltrate in psoriatic skin and synovium. Furthermore, there was no significant difference in the numbers of CLA-positive T lymphocytes in peripheral blood between psoriatic arthritis, RA and normal healthy control patients. Therefore, there does not appear to be any circulating clonal expansion of CLA-positive lymphocytes in patients with psoriatic arthritis.

The lack of association between the expression of the CLA molecule in psoriatic skin and synovium may be consistent with existing observations regarding the link between psoriasis and arthritis. For instance, there is no association between the type or distribution of skin involvement and arthritis subgroup [4]. Also a pattern of joint disease typical of mutilating psoriatic arthritis may occur without skin disease or with nail disease only [21]. In the majority of patients, the skin disease presents first and exacerbations of both skin and joint disease are only coincident in ~30% of patients [6]. We have included two patients with simultaneous exacerbations of skin and joint disease, one of whom had a higher percentage of CLA-positive lymphocytes than any other synovial sample; however, the intensity of expression was noted to be less than in skin psoriasis. In previous work, one sample of liver was found to have 40% CLA-positive T lymphocytes [15]. Our patient had a severe active synovitis in his knee, suggesting that during acute inflammation general mechanisms might override specific homing mechanisms.

E-selectin is upregulated on the vascular endothelium of inflammatory skin lesions [22] as well as other inflammatory sites [17]. The increased intensity of its expression in psoriatic skin compared with synovium found in the present study is similar to that previously reported by some [23], but not others[20]. Although the increased expression of E-selectin in skin may have bearing on the greater expression of CLA on lymphocytes in skin, there was no significant correlation between E-selectin expression and the percentage of CLA-positive lymphocytes. E-selectin also binds neutrophils via the sialyl Lewis X moiety, so its expression could reflect neutrophil diapedesis prominent in psoriatic skin, but not synovium. The reduction in mean vascular E-selectin intensity in psoriatic arthritis compared with RA was also similar to that found previously [24]. We have also studied E-selectin expression in osteoarthritis and found small quantities, similar to that found in the normal synovium of amputees [25].

The CLA antigen is not specific to psoriasis but occurs in high percentage in normal and all inflammatory skin conditions, as we have found by studying normal skin and eczema. The remarkable similarity in the percentages of CLA-positive lymphocytes in all our patients also suggests that the molecule is not specific to psoriasis, but is globally present on the majority of T lymphocytes in all skin, independent of the lymphocyte density. CLA is not present on virgin T cells, but is upregulated on a subset of T cells undergoing the virgin to memory transition in secondary lymphoid tissues [26]. Upregulation of CLA occurs in a highly regulated tissue-selective manner. For example, CLA is upregulated on over half of the T cells undergoing the virgin to memory transition in skin-associated peripheral lymph nodes, but on fewer than 10% of transitional T cells in the mucosa of small bowel. In addition, CLA expression seems to be further upregulated when memory-effector T cells are reactivated in skin, indicating that the local microenvironment at the time of T-cell activation acts to influence the homing receptor repertoire of the resultant memory-effector cells.

In conclusion, our study supports the hypothesis that the CLA population of lymphocytes is essentially specific to skin, even when skin and an extracutaneous site of inflammation occur simultaneously in the same patient, as in psoriatic arthritis. Therefore, there is no evidence to suggest that skin psoriasis and arthritis are linked through a common mechanism involving CLA T-lymphocyte interactions with E-selectin. It remains possible that skin and joint disease in psoriatic arthritis could be linked through an undiscovered adhesion receptor for a particular T-lymphocyte subset or by a common T-cell antigen. The topographic association of nail disease and distal interphalangeal joint disease still requires explanation, and examination of the distal interphalangeal joint and nailbed tissue itself may be the only way of determining related immunopathology. As skin disease usually precedes joint disease, knowledge of genetic susceptibility factors and

mechhamisms linking inflammation at separate sites may yet ennable joint disease to be predicted and prevented.

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REFERENCES

1. GBlaıdman DD. Psoriatic arthritis: recent advances in pæathhogenesis and treatment. Rheum Dis Clin North Am 199912;18:247–56.
2. MMolll JMH, Wright V. Psoriatic arthritis. Semin Arthritis RRhœum 1973;3:55–78.
3. Hdellliwell P, Marchesoni A, Peters M, Barker M, Wright VV. AA re-evaluation of the osteoarticular manifestations of psoorriasis. Br J Rheumatol 1991;30:339–45.
4. Jdonıes SM, Armas JB, Cohen MG, Lovell CR, Evison G, MMclHugh NJ. Psoriatic arthritis: Outcome of disease suubssets and relationship of joint disease to nail and skin diliseıase. Br J Rheumatol 1994;33:834–9.
5. GBlaıdman VT, Farewell VT, Nadeau C. Clinical inndiicators of progression of psoriatic arthritis: multivariatıte ırelative risk model. J Rheumatol 1995;22:675–9.
6. GBlaıdman DD, Shuckett R, Russell ML *et al.* Psoriatic arırthritis (PSA)—an analysis of 220 patients. Q J Med 199877;62:127–141.
7. WWrijght V. Psoriasis and arthritis. Ann Rheum Dis 19956;15:348–56.
8. GGerlber LH, Espinoza LR (eds) Psoriatic arthritis. New YYorık: Grune and Stratton, Inc., 1985.
9. Bdarlker JNWN. The immunopathology of psoriasis. Bdaillllière's Clin Rheumatol 1994;10b:429–38.
10. Pdanıayi GS. Immunology of psoriasis and psoriatic arırthritis. Baillière's Clin Rheumatol 1994;10a:419–28.
11. MMcHugh NJ, Laurent MR, Treadwell BLJ, Tweed JM, DDagger J. Psoriatic arthritis: clinical subgroups and hiistocompatibility antigens. Ann Rheum Dis 1987; 466:1186–8.
12. Edasttmond CJ. Genetics and HLA antigens. Baillière's CClim Rheumatol 1994;2:263–76.
13. Esspiinoza LR, Jara LJ, Espinoza CG, Silveira LH, MMaırtinez-Osuna F, Seleznick M. There is an association beetween human immunodeficiency virus infection and sppomdyloarthropathies. Rheum Dis Clin North Am 19992;18:257–66.
14. AArnıett FC, Reveille JD, Duvic M. Psoriasis and psoriatic arthritis associated with HIV infection. Rheum Dis Clin North Am 1991;17:59–78.
15. Picker LJ, Michie LS, Rott LS, Butcher EC. A unique phenotype of skin-associated lymphocytes in humans: preferential expression of the HECA-452 epitope by benign and malignant T-cells at cutaneous sites. Am J Pathol 1990;136:1053.
16. Picker LJ, Kishimoto TK, Smith CW, Warnock RA, Butcher EC. ELAM-1 is an adhesion molecule for skin-homing T cells. Nature 1991;349:796–9.
17. Bevilacqua MP, Nelson RM, Mannori G, Cecconi O. Endothelial-leukocyte adhesion molecules in human disease. Annu Rev Med 1994;45:361–78.
18. Berg EL, Yoshino T, Rott LS, Robinson MK, Warnock RA, Kishmoto TK *et al.* The cutaneous lymphocyte antigen is a skin lymphocyte homing receptor to the vascular lectin endothelial cell leukocyte adhesion molecule 1. J Exp Med 1991;174:1461–6.
19. Arnett FC *et al.* The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315–24.
20. Pitzalis C, Cauli A, Pipitone N, Smith C, Barker J, Marchesoni A *et al.* Cutaneous lymphocyte antigen-positive T lymphocytes preferentially migrate to the skin but not to the joint in psoriatic arthritis. Arthritis Rheum 1996;39:137–45.
21. O'Neill TW, Evison G, Bhalla AK. 'Pseudoarthroplastic' hand in arthritis mutilans. Br J Rheumatol 1992;31:559–60.
22. Groves RW, Allen MH, Barker JN, Haskard DO, MacDonald DM. Endothelial leucocyte adhesion molecule-1 (ELAM-1) expression in cutaneous inflammation. Br J Dermatol 1991;124:117.
23. Veale D, Rogers S, Fitzgerald O. Immunolocalization of adhesion molecules in psoriatic arthritis, psoriatic and normal skin. Br J Dermatol 1995;132:32–8.
24. Veale D, Yanni G, Rogers S, Barnes L, Bresnihan B, Fitzgerald O. Reduced synovial membrane macrophage numbers, ELAM-1 expression, and lining layer hyperplasia in psoriatic arthritis as compared with rheumatoid arthritis. Arthritis Rheum 1993;36:893–900.
25. Fairburn K, Kunaver M, Wilkinson LS, Cambridge G, Haskard D, Edwards JCW. Intercellular adhesion molecules in normal synovium. Br J Rheumatol 1993;32:302–6.
26. Picker LJ, Treer JR, Ferguson-Darnell B, Collins PA, Bergstresser R, Terstappen LWMM. Control of lymphocyte recirculation in man II. Differential regulation of the cutaneous lymphocyte-associated antigen, a tissue-selective homing receptor for skin-homing T cells. J Immunol 1993;150:1122–36.